p-ISSN 2301-4369
e-ISSN 2685-7898

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2024 Vol 11 (1) March 2024 www.medicahospitalia.rskariadi.co.id

Original Articles

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Comparison Between Placenta Accreta Index and Tovbin Score as A Predictor of Placenta Accreta Spectrum Disorders (PASD)
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Published by
Medica Hospitalia – Dr. Kariadi Hospital

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2024; Vol 11 (1)

March 2024

p-ISSN 2301-4369 e-ISSN 2685-7898

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; Vol 11 (1)
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Original Articles

1 Correlation of Duration of Antipsychotic Therapy with Hemoglobin Levels in People with Schizophrenia

Jessica Anggun Cristine Siregar[1], Innawati Jusup[2], Santoso Jaeri[2], Natalia Dewi Wardani[3]

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[2]Biology, Chemistry and Biochemistry Division of Medical Faculty of Diponegoro University, Semarang, Indonesia
[3]Psychiatry Division of Medical Faculty of Diponegoro University, Semarang, Indonesia

There was no relationship between hemoglobin levels in people with schizophrenia and duration of therapy both <2 years and ≥2 years.

7 Analysis of the Relationship between Neutrophils, Lymphocytes, and Comorbidities with Time to Death in COVID-19 Patients

Hendra Tanuwijaya, Susanthy Djajalaksana, Rezki Tantular
Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Brawijaya University / Saiful Anwar Regional General Hospital, Malang, Indonesia

There is a significant relationship between neutrophil levels and time to death, both in subjects with and without comorbidities showing the potential of neutrophil levels as a predictor of time to death in COVID-19.

13 Differences of Dyspareunia in Primipara with 2nd Degree Perineal Laceration Sutured with Rapide Polyglactin 910 and Chromic Catgut Threads

Satrio Arief Wibowo, Yuli Trisetiyono, Herman Kristanto, Putri Sekar Wiyati, Hary Tjahjanto, Erwinanto
Obstetric and gynecology Division, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

Subjects with Chromic catgut have a higher risk of experiencing dyspareunia than using Rapide Polyglactin 910 threads after 3 months of suturing.

20 Pregnancy Associated Plasma Protein-A (PAPP-A) as a Marker to Distinguish Normotensive with Early 2nd Trimester and Late 3rd Trimester Onset of Preeclampsia

Ragam Pesona Simangunsong, Herman Kristanto, Mirza Iskandar, Syarief Thaufik, Besari Adi Pramono, Arufiadi Anityo Mochtar
Department of Obstetrics and Gynecology, Faculty of Medicine, Diponegoro University / Dr. Kariadi Hospital, Semarang, Indonesia

There was a significant difference in PAPP-A levels between the second and third trimesters of early-onset preeclampsia compared to normotensive pregnancies, where PAPP-A levels were higher in the second and third trimesters of early-onset preeclampsia. Elevated PAPP-A levels in the second and third trimesters are associated with an increased risk of early-onset preeclampsia.

26 Comparison Between Placenta Accreta Index and Tovbin Score as A Predictor of Placenta Accreta Spectrum Disorders (PASD)

Willy Angga Dinata, Alini Hafiz, Arufiadi Anityo Mochtar, Julian Dewantiningrum, Putri Sekar Wiyati, Ratnasari Dwi Cahyanti
Obstetric and Gynecology Division, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

In the comparison of scoring systems, it was found that the Tovbin scoring system has almost the same sensitivity and accuracy and the same specificity in predicting Placenta Accreta Spectrum Disorder (PASD).

33 Comparison of The Effectiveness of High Intensity Laser Therapy (HILT) and Low-Level Laser Therapy (LLLT) on Improving Balance in Knee Osteoarthritis

Kukuh Wibisono, Rudy Handoyo, Erna Setiawati
Department of Physical Medicine and Rehabilitation, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

HILT improves balance score better than LLLT.

38 Relationship between Serum Malondialdehyde (MDA) Levels with Seizure Frequency in Epilepsy Patients with Combination of Phenytoin and Valproic Acid

Aji Noegroho, Aris Catur Bintoro, Dwi Pudjonarko
Neurology Division, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

There is a significant relationship between the frequency of seizures with the length of treatment and the age of onset of epilepsy.

45 Characteristics and Risk Factor of Multidrug-Resistant-Organism Infection in the Pediatric Intensive Care Unit of Dr. Kariadi Hospital Semarang

Nahwa Arkhaesi[1], Moh. Supriatna[1], Yusrina Istanti[1], Desvita Sari[2], Safira Rizqi Azzahra[3]
[1]Department of Pediatric, Medical Faculty of Diponegoro University / Dr. Kariadi Hospital Semarang, Indonesia
[2]Department of Clinical Microbiology, Medical Faculty of Diponegoro University / Dr. Kariadi Hospital Semarang, Indonesia
[3]Medical Faculty of Diponegoro University, Semarang, Indonesia

Klebsiella pneumoniae is the most common germ found from culture isolates and respiratory tract infection is the most common diagnosis. The use of mechanical ventilators and length of stay in the PICU are risk factors for MDRO infection.

53 Effectiveness of Foot Exercises Together with the Hydrotherapy Program on Blood Sugar Levels in Elderly People without Diabetes

Edy Nuswantara Putra[1], Yuswo Supatmo[2], Erna Setiawati[3], Marijo[4]
[1]Department of Medicine, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[2]Department of Physiology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[3]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[4]Department of Anatomy, Faculty of Medicine, Diponegoro University

Simple exercise activities such as foot exercises together with hydrotherapy have been proven to reduce blood sugar levels in healthy elderly populations without diabetes.

58 The Relationship between the Duration of Suffering from Diabetes and HbA1c Levels with the Degree of Liver Stiffness in Type 2 Diabetes Mellitus Patients

Faza Khilwan Amna[1], Maya Nuriya Widyasari[1], Hery Djagat Purnomo[2], Frederica Mardiana Wahyuni[1], Bambang Satoto[1], Hermina Sukmaningtyas[1]

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[2]Gastroenterohepatology Division of Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

There is a relationship between liver stiffness and HbA1c levels but there is no relationship between liver stiffness and the duration of suffering from type 2 DM.

64 The Effect of Mckenzie Exercise to Increase Craniovertebral Angle in Forward Head Posture of Adolescent

Raras Hestina Laksmi, Nitaya Putri Nur Hidayati, Yuliana Ratmawati
Program Study of Physiotherapy, Health Polytechnic of Ministry of Health Surakarta, Indonesia

McKenzie's exercise can affect to increasing the craniovertebral angle in the forward head posture of adolescents.

71 Effectiveness of Kelly Plication Method on Clinical Improvement in Stress Urinary Incontinence Patients

Puspitasari Notohatmodjo[1], Besari Adi Pramono[2], Inu Mulyantoro[3], Herman Kristanto[2], Dewi Astri Purnaningtyas[4], Arufiadi Anityo Mochtar[4], Erwinanto[4]
[1]1Obstetric and Gynecology Department, Medical Faculty of Diponegoro University Semarang, Indonesia
[2]Fetomaternal Subdivision, Obstetrics and gynecology Department, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia
[3]Fertility Subdivision, Obstetrics and gynecology Department, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia
[4]Urogynecology Subdivision, Obstetrics and gynecology Department, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

Kelly's plication method is effective in treating SUI.

79 The Correlation between Volatile Organic Compounds (VOC) with Leukotriene B4 and Eosinophil Counts in Chronic Obstructive Pulmonary Disease Patients

Andrew Santosa, Ngakan Putu Parsama Putra, Aditya Sri Listyoko, Arinto Yudi Ponco Wardoyo, Nanik Setijowati
Department of Respiratory and Pulmonology, Faculty of Medicine University of Brawijaya / Dr Saiful Anwar General Hospital, Malang, Indonesia

There is a correlation between VOC and LTB4 in COPD patients.

89 The Effectiveness of E-Backnshou Exercise to The Improvement of Neck, Shoulder and Back Pain in Computer Vision Syndrome Patient

Hari Peni Julianti, Trilaksana Nugroho, Tanti Ajoe Kesoema, Neni Susilaningsih, Fifin Luthfia Rahmi, Maharani Rizka Pritadesya
Faculty of Medicine Diponegoro University, Semarang, Indonesia

The effectiveness of 20-20-20 rule and E-BACKNSHOU exercise is better than the 20-20-20 rule alone on treating neck, shoulder and back pain in CVS patient.

94 Prenatal, Perinatal and Postnatal Risk Factors from Mother and Child to The Incidence of Epilepsy

Susan Megawati Sibuea, Endang Kustiowati, Maria Immaculata Widiastuti Samekto, Dodik Tugasworo, Aris Catur Bintoro, Elta Diah Pasmanasari
Department of Neurology, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia

Prenatal factors of the mother which is maternal age during pregnancy, perinatal and postnatal factors of the child which are low birth weight, surgical birth, and head trauma at the age of less than 6 years are risk factors that influence the occurrence of adulthood epilepsy.

100 Functional Capacity COVID-19 Survival among Workers in Koja Public Health Center

Alra Mistivani[1], Melinda Harini[1], Widjajalaksmi Kusumaningsih[1], Peggy Sunarjo[1], Budiati Laksmitasari[1], Nelfidayani[1], Rizky Kusuma Wardhani[1], Ni Luh Made M J[1], Ratna Ekawati[1], Edvina[1], Prisca Ockta[1], Adhitya[1], Reni Rozanti[1], Ricky Fakhrazi[1], Felix Leo[1], Novita Suprapto Wati[2], Endang Sri Wahyuningsih[2], Dwi Oktavia[2], Rofi Yuliandra[2], Vinnaria Astuty[3], Sri Puji Wahyuni[3], Julieta Tantri[3], Gilang Rama Putra[1]
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[2]DKI Jakarta Provincial Health Office, Jakarta, Indonesia
[3]Koja District Health Center, Jakarta, Indonesia

Despite being COVID-19 survivors, the workers at the Koja Public Health Center have good functional capacity.

107 Effect of Triamcinolone Trigger Point Injection on Changes in TNF-α Levels and Oswestry Disability Index (ODI) Scores Non-Specific Low Back Pain (LBP) Patients

Mohamad Fakih, Suryadi, Dodik Tugasworo, Dwi Pudjanarko, Amin Husni, Trianggoro Budisulistyo, Arinta Puspitawati
Neurology Department Faculty of Medicine, Diponegoro University/ Kariadi Hospital Semarang, Indonesia

There is a significant difference in changes in TNF-α levels and ODI scores before and after Triamcinolone trigger point injection.

Case Report

113 Rehabilitation of A Child with Low Endurance in the Recovery Phase of Guillain-Barré Syndrome

Budiati Laksmitasari[1], Johanes Putra[2], Luh Karunia Wahyuni[1], Rizky Kusuma Wardhani[1]
[1]Department of Physical Medicine and Rehabilitation, Dr Cipto Mangunkusumo Hospital, Faculty of Medicine-Indonesia University, Jakarta, Indonesia
[2]Physical Medicine and Rehabilitation Recidency Program, Faculty of Medicine-Indonesia University, Jakarta, Indonesia

Rehabilitation management in children with low cardiorespiratory endurance due to the sub-acute phase of GBS could help them regain their activity and participation during the recovery phase.

119 Follicular Ameloblastoma of Maxillary: A Case Report

Athalaila Azzahrasukma Sakuntala[1], Efika Choirunisa[1], Septa Santiya Arini[1], Johanna Kezia Prajogo[1], Muhammad Reza Pahlevi[2]
[1]Dentistry Department, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[2]Oral and Maxillofacial Surgery Clinic, Dr. Kariadi Hospital, Semarang, Indonesia

In principle, the treatment for ameloblastoma is resection of the involved bone, as in this case the action taken is a maxillectomy. Maxillectomy can result in facial and oral cavity deformities characterised by facial disfigurement and alterations in oral functionality.Therefore, maxillary reconstruction is needed to treat maxillary defects after surgical procedures involving the loss of part or all of the maxilla.

125 Case Series : Orbital Complications in Pediatric Rhinosinusitis

Anna Mailasari Kusuma Dewi, Desy Iriani
Otorhinolaryngologist - Head and Neck Surgery Departement, Faculty of Medicine Diponegoro University / Dr. Kariadi Hospital, Semarang, Indonesia

Acute rhinosinusitis with orbital complications can caused by adenoid hypertrophy and dental infection. Medical treatment with adequate antibiotic followed by FESS, abscess drainage, adenoidectomy and odontectomy give an optimal result.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; Vol 11 (1)
March 2024

Editorial

International scientific publications are considered as one of productivity benchmarks of world-class universities. However, Indonesian universities still face challenges in increasing publications quantity and quality, including ownership of scientific journals of international reputation. Therefore, collaborations between domestic and overseas universities are continuously encouraged to improve the scientific publications performance.

In terms of quantity, the number of Indonesian scientific publications has increased rapidly in the last seven years. In 2021, the number of publications reached 50,000 publications, thereby boosting Indonesia's scientific publication ranking from 56th to 21st in the world.

Based on Scimago Journal & Country Rank data, the number of Indonesian scientific publications in Scopus indexed journals were 43,300 documents in 2022. This number places Indonesia in 25th out of 243 countries according to the number of publications of scientific works in Scopus indexed journals.

The publishing ranking of Indonesian scientific papers is still inferior to several developing countries, such as Brazil and Malaysia. In 2021, Brazil was ranked 14th in the world as it has published 92.890 scientific works indexed by Scopus. Malaysia was ranked 23rd or two rank higher than Indonesia. There were 44,439 scientific publications from Malaysia indexed by Scopus. Meanwhile, China was known as the country with the most scientific publications in the world in 2022 as there were 1.004.745 publications in 2022.

Scientific journals are often considered as an important benchmark in assessing a country's research productivity. Scientific journals can also improve the quality of research along with the peer review process. So, it is time for the Medica Hospitalia journal to rise and become a Scopus indexed journal. This is a challenge for the academic community to submit research articles of increasingly high quality.

Let's build our nation together through an activity that we are closely involved in, namely research.

Regards,

Editor

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 1–6

OPEN ACCESS

Original Article

Correlation of Duration of Antipsychotic Therapy with Hemoglobin Levels in People with Schizophrenia

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.908

Accepted: January 16th, 2023
Approved: February 16th, 2024

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Publisher's Note:
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Abstract

Background : Schizophrenia is a serious mental disorder with various unknown causes accompanied by a collection of positive symptoms, negative symptoms, disorganization in thinking, speaking or movement and cognitive dysfunction. The therapeutic modality used to treat these symptoms is antipsychotic therapy. Over a certain period of time, the use of antipsychotics can cause hematological syndrome which affects the process of red blood cell formation and hemoglobin levels. Low hemoglobin levels can worsen neuronal function in the brain, thereby aggravating symptoms in schizophrenia. The aim of this study was to analyzing the relationship between duration of antipsychotic therapy <2 years and ≥2 years with hemoglobin levels in schizophrenia patients.
Methods : This research is an analytical observational study with a cross-sectional approach in which research subjects were obtained using a consecutive sampling method from medical records of patients with schizophrenia (ODS) at RSJD Dr. Amino Gondohutomo Semarang (n=68) divided into 2 groups consisting of patients with a duration of therapy <2 years and a duration of therapy ≥2 years. The relationship between duration of antipsychotic therapy and hemoglobin levels was analyzed using unpaired t-test.
Results : The mean hemoglobin value for people with schizophrenia in the group with a duration of therapy <2 years is 14.09, while that in the group with a duration of therapy ≥2 years is 14.06 with a p value = 0.928.
Conclusion : There was no relationship between hemoglobin levels in people with schizophrenia and duration of therapy both <2 years and ≥2 years.

Keywords : Antipsychotic, Hemoglobin, Hematology, Schizophrenia.

INTRODUCTION

Schizophrenia is a serious mental disorder with various unknown causes, accompanied by a collection of positive symptoms, negative symptoms, disorganization in thinking and cognitive dysfunction. WHO states that around 0.7% people with schizophrenia (ODS) are adults with an age range of 15–35 years, and according to the 2018 National Basic Health Research Report (RISKESDAS) the average prevalence (per mile) of households that have members with schizophrenia mental disorders in Indonesia is 0.67%. Meanwhile, there are 8.7% of the population suffering from schizophrenia in Central Java.[1,2] The therapy used as the main modality to treat schizophrenia symptoms is antipsychotic therapy categorized into 2 groups; class I (typical) antipsychotics, which have higher effectiveness in treating positive symptoms of schizophrenia and class II (atypical) antipsychotics, which are effective in treating both positive and negative symptoms.[3] Antipsychotic therapy is medications for long term use or with repeated administration however, long-term use of antipsychotic therapy may cause intoxication of the blood and neurons. Studies suggest the emergence of hematological syndromes provoked by antipsychotics include blood dyscrasias, pancytopenia and bicytopenia. Dyscrasia refers to abnormalities in the values of red blood cells, white blood cells and platelets which then cause manifestations such as anemia, leukopenia and thrombocytopenia.[4,5] One of the manifestations - anemia can be assessed by looking at the hemoglobin level as a component of red blood cells transporting oxygen in the blood to all organs, tissues and cells, including neuron cells in the brain. Disruption of the process of forming red blood cells in the bone marrow can result in a decrease in blood hemoglobin levels which in turn provoke worsening of neuronal function in the brain. In schizophrenia, this condition can last for a long time, thus making the symptoms worse.[6,7]

Hematological syndrome due to antipsychotic therapy is a rare event, but important because it can be fatal or result in mortality (1–2/100,000 cases with a mortality of 8–17%).[8] Therefore, this study was conducted to find out how long antipsychotic therapy is related to Hemoglobin levels in schizophrenic patients.

METHODS

This research is an analytical observational study with a cross-sectional design assessing the duration of antipsychotic therapy on hemoglobin levels seen at one time. Subjects were recruited using a consecutive sampling method from medical records of people with schizophrenia hospitalized in the period of January to December 2019 at RSJD Dr. Amino Gondohutomo Semarang. The total number of research subjects was 68 medical records that met the inclusion criteria. The research subjects were divided into 2 groups, namely 34 subjects with a duration of therapy <2 years and 34 subjects with a duration of therapy ≥2 years. The inclusion criteria were patients aged 21 to 50 years with a diagnosis of schizophrenia based on medical records and receiving standard schizophrenia management therapy. The exclusion criteria were patients receiving benzodiazepam therapy and patients with comorbid physical illnesses.

Data analysis using the SPSS version 26.0 program included descriptive analysis and relationship testing. Normality test was conducted hemoglobin level and subject age data. Research was carried out using the Shapiro Wilk test. Data on length of therapy with age were explained using the unpaired t-test because the data obtained were normally distributed. Data on length of therapy with BMI, address, gender, diagnosis, therapy history, education level and marital status were analyzed using the Chi-square test. Data on length of antipsychotic therapy and hemoglobin levels were analyzed using unpaired t-test. All results were considered statistically significant if the p value was < 0.05 with a 95% confidence interval.

Research protocol had been approved by the issuance of Ethical Clearance No. 188/EC/KEPK/FK-UNDIP/VIII/2020 from the Health Research Ethics Commitee (KEPK) of Medical Faculty of Diponegoro University and Ethics Test Certificate Number 420/9774 by the Health Research Ethics Team of RSJD Dr. Amino Gondohutomo, Central Java.

RESULTS

Demographic Characteristics

The demographic characteristics of the 68 research subjects include age, body mass index (BMI), address, gender, education level and marital status (Table 1).

Table 1 shows 68 research subjects have a mean age of 32.82 ± 7.11 years, with a mean BMI value of 21.69 ± 2.36. The distribution of research subjects based on nutritional status consist of 5 underweight (7.35), 42 normoweight (61.76), 19 overweight (27.94) and 2 obese (0.29). The research subjects consist of 45 male (66.17) and 23 female (33.82). Most of research subjects come from outside Semarang (52 subjects or 76.47%), are single (44 subjects or 64.70%) and graduated from junior high school (29 subjects or 42.64%).

Table 2 shows the distribution of research subjects based on diagnosis and type of antipsychotic used. The majority of schizophrenia diagnoses involve people with paranoid schizophrenia (32 subjects or 47.05%), unspecified schizophrenia (22 subjects or 32.35%), catatonic schizophrenia (11 subjects or 14.70%) and heberphrenic schizophrenia (4 subjects or 5.88%). In terms of antipsychotic use, 38 subjects (55.88) used

TABLE 1
Demographic Characteristics of Research Subjects

Variable	Mean ± SD n (%)	Mean ± SD n (%)		*p**
		<2 Year	≥2 Year	
Age (year)	32.82 ± 7.11	33.24 ± 7.41	32.41 ± 6.89	0,637[a]
IMT (kg/m^2)	21.69 ± 2.36	21.42 ± 2.14	21.95 ± 2.56	0,951[b]
Underweight	5 (7.35)	3 (0.44)	2 (0.29)	
Normoweight	42 (61.76)	20 (29.41)	22 (32.35)	
Overweight	19 (27.94)	10 (14.70)	9 (13.23)	
Obesity	2 (0.29)	1 (0.14)	1 (0.14)	
Address				
Semarang	16 (23.52)	5 (7.35)	11 (16.17)	0,086[b]
Outside Semarang	52 (76.47)	29 (42.64)	23 (33.82)	
Gender				
Male	45 (66.17)	20 (29.41)	25 (36.76)	0,200[b]
Female	23 (33.82)	14 (20.58)	9 (13.23)	
Education level				
Elementary School	13 (19.11)	6 (8.82)	7 (10.29)	0,946[b]
Junior High School	29 (42.64)	15 (22.05)	14 (20.58)	
Senior High School & College	26 (38.23)	13 (19.11)	13 (19.11)	
Marital Status				
Married	15 (22.05)	8 (11.76)	7 (10.29)	0,915[b]
Divorced	9 (13.23)	4 (5.88)	5 (7.35)	
Single	44 (64.70)	22 (32.35)	22 (32.35)	

Note: *significant (p<0,05); [a]unpaired t-test; [b]*Chi Square*

atypical antipsychotics consisting of 23 subjects with risperidone therapy (33.82%), 11 subjects with clozapine therapy (16.17%) and 4 subjects with combination therapy with risperidone and clozapine (5.88%), combined antipsychotics in 29 subjects (42.64%) and typical antipsychotics in the form of haloperidol in 1 subject (1.47%).

Characteristics of research subjects in the two research groups show no significant differences in all variables involving age (p=0.637), BMI (p=0.951), address (p=0.086), gender (p=0.200), education level (p=0.946), marital status (p=0.915), diagnosis (p=0.430) and type of antipsychotic (p=0.206).

Analysis of the Relationship between Duration of Antipsychotic Therapy and Hemoglobin Levels

The following table shows the relationship analysis between duration of antipsychotic therapy and hemoglobin levels, in which 68 research subjects are grouped based on length of therapy involving <2 years (34) and ≥2 years (34).

Most subjects have normal hemoglobin levels involving 30 subjects in the <2 years group (44.11%) and 23 subjects in the ≥2 year group (33.82%), while subjects experiencing decreased hemoglobin levels are in the <2 year group as many as 4 subjects (5.88%) and 11 subjects in the ≥2 year group (16.17) with p value= 0.041 which is statistically significant.

T-test analysis of the duration of antipsychotic therapy with hemoglobin levels shows no significant relationship in either the group with <2 year therapy or the group with ≥2 year therapy (p > 0.05).

TABLE 2
Research subject distribution

Variable	Mean ± SD n (%)	Mean ± SD n (%)		*p**
		<2 Year	≥2 Year	
Diagnose				
Paranoid Schizophrenia	32 (47.05)	13 (19.11)	19 (27.94)	0.430[b]
Heberphrenic Schizophrenia	4 (5.88)	22 (2.94)	2 (2.94)	
Catatonic Schizophrenia	10 (14.70)	5 (7.35)	5 (7.35)	
Schizophrenia Unspesified	22 (32.35)	14 (20.58)	8 (11.76)	
Types Antipsychotic				
Typical Antipsychotic – HLP	1 (1.47)	1 (1.47)	0 (0)	0.206[b]
Atipikal Antipsychotic	38 (55.88)	22 (32.35)	16 (23.52)	
Risperidon	23 (33.82)	15 (22.05)	8 (11.76)	
Klozapin	11 (16.17)	6 (8.82)	5 (7.35)	
Risperidon – Klozapin	4 (5.88)	1 (1.47)	3 (4.41)	
Combination	29 (42.64)	11 (16.17)	18 (26.47)	

Note: *significant (p<0.05); [b]*Chi Square*

TABLE 3
Description of hemoglobin levels in each group

Variable	<2 Year n (%)	≥2 Year n (%)	*p**
Decreased	4 (5.88)	11 (16.17)	0.041[b]
Normal	30 (44.11)	23 (33.82)	

Note: *significant (p<0.05); [b]*Chi Square*

TABLE 4
Relationship between duration of antipsychotic therapy and hemoglobin levels

Variable	<2 Year Mean ± SD Median (Min–Max)	≥2 Year Mean ± SD Median (Min–Max)	*p**
Hemoglobin	14.09 ± 1.49	14.06 ± 1.16	0.928[a]
(gr/dl)	14.20 (10.8–16.5)	13.95 (11.4–16.2)	

Note: *significant (p<0.05); [a]unpaired t-test

DISCUSSION

The mean age of the research subjects showed the incidence of schizophrenia in productive age (32.82 ± 7.11). This can be explained by various stressors arising in productive age range, such as family problems, financial problems, educational or work problems as well as the burden of responsibility affecting an individual's

emotional development.[9]

Nutritional status of research subjects are categorized into 4 groups based on BMI involving underweight (BMI <18.5), normoweight (BMI 18.5–22.9), overweight (23–24.9) and obesity (BMI >25).[10] More than half of the subjects had good nutritional status and are categorized as normoweight, which explains that there is no significant relationship between the length of antipsychotic therapy and nutritional status in people with schizophrenia. Nutritional status is influenced by several factors such as nutritional intake or eating patterns, daily activities, socio-economic status, environmental conditions and fat percentage.[11,12]

Based on marital status, it was found that more than half of the research subjects are single. Schizophrenia that appears in early adulthood can affect social abilities disrupting patient's ability to build relationships such as marriage.[9,13] Similarly, previous study conducted by Mawar DY *et al* (2017) at the Sambang Lihum Mental Hospital, South Kalimantan shows more than half of the research subjects with schizophrenia are at the age range of 17 to 40 years old and single.

Based on subjects characteristics, the majority of patients are male sugggesting that there is a different response between men and women to antipsychotic therapy. Previous studies show slower disease progression in women than men. There is a neuroprotective function of the hormone estrogen in women.[14] There are different pharmacokinetics in women such as slower absorption and higher body fat increasing antipsychotics accumulation in adipose tissue which in turn increasing the half-life of medications. Slower CYP1A2 activity and drug elimination in women prolong drug accumulation in the body. Thus, women show better response to antipsychotic therapy than men do.[5,16]

In this study, class II antipsychotics, such as risperidone and clozapine, are the main therapeutic modality for schizophrenia. The most common side effect of clozapine is agranulocytosis, so patients with clozapine therapy are advised to carry out differential count laboratory checks every week during the first 6 months of therapy. Higher effectiveness in treating positive and negative symptoms as well as a lower incidence of extrapyramidal side effects than class I antipsychotics due to a more selective mechanism of action in inhibiting dopamine receptors in the cortical and limbic areas rather than the nigrostriatal pathway could be the reason why generation II antipsychotics are preferred as therapy.[12,17]

This study analyzed the relationship between the duration of antipsychotic therapy and the hemoglobin levels of people with schizophrenia which are categorized found a difference in the mean value of hemoglobin levels in the group with duration of therapy both <2 years and ≥2 years, but there is no statistically significant relationship in both groups. The results of this study are in accordance with previous research which reported that no significant relationship was found with hemoglobin levels while in a different study it was also found that there is no significant relationship between red blood cell parameters and duration of antipsychotic therapy and BMI.[11,18] Anemia which can be assessed by a decrease in hemoglobin levels <12 gr/dL or red cells <4.5x106/uL is the rarest antipsychotic therapies-related abnormality in people with mental disorders such as schizophrenia.[19,4] However, previous study conducted by Jimmy L *et al* (2015) showed a high incidence of anemia in the first 2 years of therapy, although it was later stated that there were various factors playing role in the incidence of anemia such as the preferred antipsychotic medication, physical condition, poor lifestyle and nutritional intake.[20,21]

The normal range of hemoglobin levels in both groups could be caused by improved toxicity. Improvement can occur when antipsychotic therapy is stopped or replaced. However, it was found that the number of research subjects experiencing a decrease in hemoglobin levels is greater in the ≥2 year group. This is related to the chronic conditions experienced, the drugs consumed and lifestyle.[4,21] This is different from other research which states that the lower mean value of hemoglobin levels in the <2 year group could occur due to the toxicity process at the beginning of therapy. Based on previous studies, clinical symptoms appeared around 4 to 5 weeks after the commencement of therapy.[11]

Study Limitation

The hemoglobin level data was obtained from medical records where the blood tests were not carried out at the same time and analysis of several factors possibly influencing hemoglobin were not carried out, such as gender grouping in female samples, so the age group must be taken into account when carrying out blood tests, patient's diet and lifestyle. Differences in antipsychotic therapy received by each subject can also bias the results. Suggestions for further research are to control data variations, especially subject demographic data.

CONCLUSION

There is no significant relationship between duration of antipsychotic therapy <2 years and ≥2 years and hemoglobin levels in people with schizophrenia.

It is necessary to control variations in subject demographic data and pay attention to other factors that can influence blood hemoglobin levels such as the time of blood sampling, diet and lifestyle.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 7–12

OPEN ACCESS

Original Article

Analysis of the Relationship between Neutrophils, Lymphocytes, and Comorbidities with Time to Death in COVID-19 Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.932

Accepted: February 27th, 2023
Approved: December 19th, 2023

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Publisher's Note:
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Abstract

Background : COVID-19 caused 5.4 million deaths in 2021. Various parameters such as comorbidities and laboratory findings are known to be predictors of death in COVID-19, but these findings differ in each country, and their relationship to time of death has not been widely studied. This study was conducted to determine the relationship between levels of neutrophils, lymphocytes, neutrophil to lymphocyte ratio (NLR), and comorbidities with time to death in COVID-19.
Methods : A retrospective cohort study was conducted from April 2020 to September 2021 in the COVID-19 Inpatient Room at RSUD dr. Saiful Anwar Malang with 300 COVID-19 patient subjects aged 18 years and over. Data on comorbidities (hypertension, CAD, HF, obesity, COPD, CKD, cancer), time to death, and laboratory were taken from medical records. The Kolmogorov-Smirnov test, Chi square test and Mann Whitney test were carried out to analyze the data.
Results : There was a significant relationship between neutrophil levels and time to death, as well as a significant difference in neutrophil levels in the group with time to death >48 hours with comorbidities compared to <48 hours with and without comorbidities. There was a significant difference in lymphocyte levels and NLR in patients with comorbidities with time to death <48 hours and >48 hours ($p < 0.05$).
Conclusion : There is a significant relationship between neutrophil levels and time to death, both in subjects with and without comorbidities showing the potential of neutrophil levels as a predictor of time to death in COVID-19.

Keywords : COVID-19, time to death, comorbidities, neutrophils, lymphocytes

INTRODUCTION

COVID-19 caused around 5.4 million deaths worldwide in 2021. Although most COVID-19 sufferers experience mild flu-like symptoms, others can experience respiratory distress which can lead to a serious condition.[1] Various factors can be predictors of COVID-19 mortality such as comorbidities and laboratory parameters. However, studies related to predictors of COVID-19 mortality show different findings in various countries.[2]

Neutrophils and lymphocytes are laboratory parameters that have been proven to be associated with the severity of COVID-19. This laboratory parameter is also represented by the neutrophil to lymphocyte ratio (NLR). Neutrophils specifically have also been linked to the severity of COVID-19 via increased inflammation and thrombosis due to the production of neutrophil extracellular traps (NET). Studies show a significant relationship between NLR and the severity of COVID-19,[3] as well as an increased risk of mortality with increasing NLR.[4] Apart from NLR, previous studies have shown a significant association between lymphocytes and an increased risk of death in COVID-19 patients.[5] These findings demonstrate the importance of the association of neutrophils and lymphocytes with mortality in COVID-19.

Various studies on predictors of COVID-19 mortality have been conducted in various countries.[6–8] However, it is necessary to examine more deeply in this mortality case, which factors are predictors of time of death. In this retrospective cohort study, the relationship between time of death and comorbidities, as well as laboratory parameters such as neutrophils, lymphocytes and neutrophil-to-lymphocyte ratio (NLR), were studied.

METHODS

This retrospective study was conducted in the COVID-19 Inpatient Room (incovit) RSUD Dr Saiful Anwar Malang from April 2020 to September 2021. The data selected is data from subjects diagnosed with COVID-19, complete medical record data, and the final outcome of treatment (survived or non-survived). Data analysis carried out was time to death after hospital admission (<48 hours and >48 hours), comorbidity, and laboratory. Conditions categorized as COVID-19 comorbidities according to CDC recommendations are heart disease (hypertension, CAD, and HF), obesity (BMI > 30 kg/m^2), COPD, CKD, and cancer.[9] The laboratory data analyzed were neutrophils and lymphocytes with number classification based on a reference tool (XE-2100, Sysmex, Germany).[10] Neutrophil to lymphocyte ratio (NLR) was obtained by dividing the percentage of neutrophils by lymphocytes. Normality analysis of data distribution was carried out using the Kolmogorov-Smirnov test. Categorical data were analyzed using the Chi Square test, numerical data were analyzed using the Mann Whitney test. Statistical analysis used the Statistical Package for the Social Sciences (SPSS).

RESULTS

In this study, there were 300 patient data divided into time to death (<48 hours & >48 hours) and comorbidities (yes & no). There were 124 patients with time to death <48 hours, and 176 patients with time to death >48 hours after admission. 112 patients had no comorbidities and 188 patients had comorbidities. Data on the distribution of subjects based on time to death and comorbidities are shown in Table 1.

Analysis of the percentage of neutrophils, lymphocytes and NLR was carried out in this study. The mean percentage of neutrophils in all subjects was 81.90 ± 8.22. The mean percentage of lymphocytes in all subjects was 11.55 ± 6.57. Meanwhile, the average NLR is 10.58 ± 8.71. There was no significant difference in neutrophils, lymphocytes, and NLR related to the presence or absence of comorbidities. However, there was significant difference in the percentage of neutrophils in the subject groups with different times of death shown in Table 2.

Classification of neutrophil and lymphocyte levels did not show any subjects with neutropenia or lymphocytosis in this study. There were 50 subjects with normal neutrophil percentages and 250 subjects with neutrophilia. Regarding lymphocyte classification, there were 75 subjects with normal lymphocyte percentages and 225 subjects with lymphopenia. There were significant differences in neutrophil classification in subjects with different times of death. Data can be seen in Table 3.

Data analysis then continued with differentiating groups between time of death and comorbidity. There were 21 patients with time to death <48 hours without comorbidities, 103 patients with time to death <48 hours with comorbidities, 91 patients with time to death >48 hours without comorbidities, and 85 patients with time to death >48 hours with comorbidities. Neutrophil levels in patients with time to death >48 hours with comorbidities were significantly different compared to patients with time to death <48 hours with and without comorbidities ($p < 0.05$). Lymphocyte levels and NLR in patients with time to death >48 hours with comorbidities were significantly different compared to patients with time to death <48 hours with comorbidities ($p < 0.05$) (Table 4).

There was a pattern of decreasing mean neutrophils in patients with time to death <48 hours without and with comorbidities (83.61 vs 83.13) and continued in patients with time to death >48 hours without and with comorbidities (81.98 vs 79.91). In lymphocytes, there was a pattern of a slight decrease in

TABLE 1
Subject division based on time of death and comorbidities

Parameter		Time of Death		*p**
		<48 hours (N=124)	>48 hours (N=176)	
Comorbidities	Yes	103	85	0.001*
	No	21	91	

*Statistically significant differences (p<0.05)

TABLE 2
Neutrophil, lymphocyte and NLR levels based on time of death

Parameter (Mean±SD)	Time of Death		*p**
	<48 hours (N=124)	>48 hours (N=176)	
Neutrofils (%)	83.21 ± 7.41	80.98 ± 8.64	0.044*
Lymphocytes (%)	10.50 ± 5.78	12.29 ± 7.01	0.056
NLR	11.88 ± 10.72	9.67 ± 6.85	0.050

*Statistically significant differences (p<0.05)

TABLE 3
Classification of neutrophils and lymphocytes based on time of death

Parameter		Time of Death		*p**
		<48 hours (N=124)	>48 hours (N=176)	
Neutrofils (%)	Normal	13	37	0.016*
	Neutrophilia	111	139	
Lymphocytes (%)	Normal	27	48	0.279
	Lymphopenia	97	128	

*Statistically significant differences (p<0.05)

mean lymphocytes in patients with time to death <48 hours without and with comorbidities (10.63 vs 10.47) and continued with an increase in patients with time to death >48 hours without and with comorbidities (11.86 vs 12.77). A pattern of decreasing mean NLR was found in patients with time to death <48 hours without and with comorbidities (14.18 vs 12.68) and in patients with time to death >48 hours without and with comorbidities (10.03 vs 9.27).

DISCUSSION

In this study, a significant relationship was found between the presence or absence of comorbidities and time to death (p <0.05). Various studies also show similar findings related to comorbidities and mortality rates in COVID-19 patients. A study by Djaharuddin *et al*. shows that comorbidities such as diabetes, heart disease and hypertension are the most frequently found comorbidities in COVID-19 death cases, with more than 50 percent of sufferers of these death cases having two or more comorbidities.[11] A meta-analysis study in 2021 also showed similar results, with hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and heart disease as the comorbidities most frequently associated with mortality in COVID-19 patients. The presence or absence of comorbidities is an important factor related to COVID-19 mortality due to the occurring pathological process. Metabolic syndrome comorbidities such as hypertension and diabetes are conditions that can

TABLE 4
Neutrophil and lymphocyte levels based on time of death and comorbidities

	Comorbidities	Time of Death		*p**
		<48 hours (N=124)	>48 hours (N=176)	
Neutrophil Percentage (Mean ± SD)	Yes	83.13 ± 7.05	79.91 ± 8.57[ab]	0.032*
	No	83.61 ± 9.16	81.98 ± 8.64	
Lymphocytes Percentage (Mean ± SD)	Yes	10.47 ± 5.23	12.77 ± 6.89[b]	0.111
	No	10.63 ± 8.10	11.86 ± 7.12	
NLR (Mean ± SD)	Yes	11.42 ± 10.28	9.27 ± 7.27[b]	0.089
	No	14.18 ± 12.68	10.03 ± 6.45	

[a](p<0.05 vs <48 hours without comorbidities); [b](p<0.05 vs <48 hours with comorbidities)

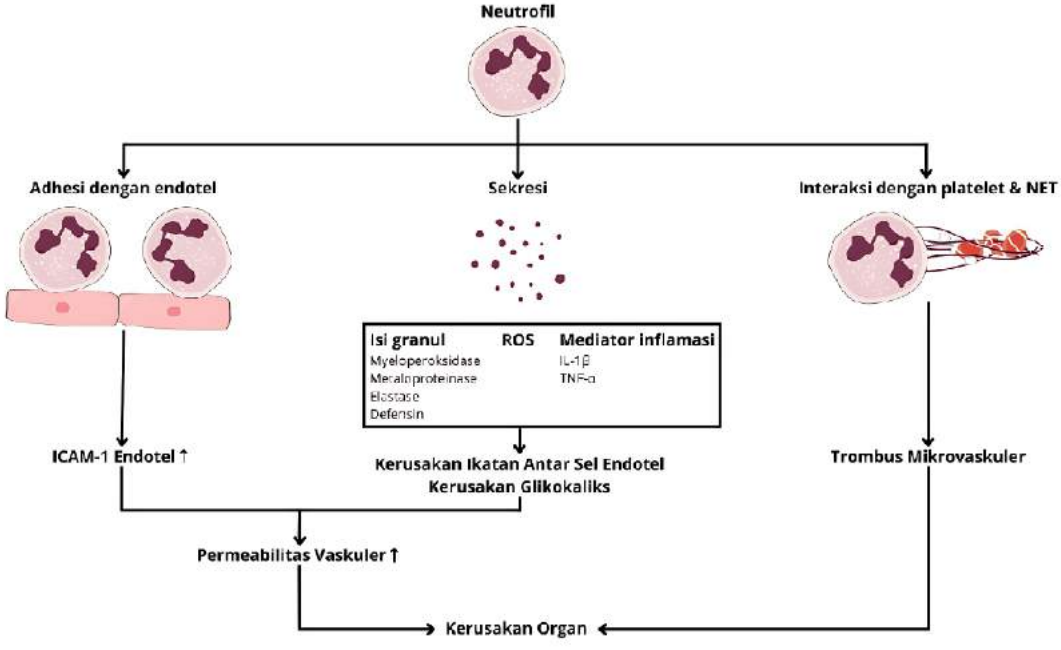

Figure 1. Pathophysiology of neutrophils in causing organ damage which leads to mortality. Neutrophil adhesion to the endothelium increases ICAM-1 which leads to increased transendothelial permeability, while neutrophil secretion results in increased paraendothelial permeability through damage to the glycocalyx and inter-endothelial bonds. The interaction of neutrophils with platelets and NET secretion causes microvascular thrombi which can lead to vascular obstruction. ICAM1: intercellular adhesion molecule-1; ROS: reactive oxygen species; IL: interleukin; TNF: tumor necrosis factor; NET: neutrophil extracellular traps. Licensed by Hendra Tanuwijaya

cause pathological conditions in various aspects, such as chronic inflammatory conditions, as well as vascular disorders that can contribute to COVID-19 mortality. Heart disease and COPD can also contribute to the process of dyspnea which is one of the main symptoms of COVID-19 which also contributes to the mortality of COVID-19 patients.[12]

In this study, significant differences in neutrophil levels were found in groups with different times of death (p<0.05). Apart from that, there were also significant differences in the categories of neutrophil levels (normal and neutrophilia) in groups with different times of death (p<0.05). Further analysis by dividing the subject groups based on time of death as well as comorbidities also showed significant differences in neutrophil levels (p<0.05). A previous study by Siahaan *et al*. shows similar results. In this study, neutrophil levels were significantly related to the clinical outcomes of COVID-19 patients.[13]

Previous studies also indirectly showed similar findings, where NLR was known to be significantly related to, as well as being a predictor and independent risk factor for mortality in COVID-19 patients.[4,14,15]

The findings regarding neutrophil levels in this study may also be related to its specific pathophysiology in COVID-19. Increased neutrophils have been proven to be one of the pathophysiology of COVID-19 with severe symptoms.[16] The function of neutrophils is to produce NETs which have also been shown to increase in COVID-19 patients.[17] Studies have proven that NETs have not only been shown to increase in the plasma of COVID-19 patients, but are also associated with severity, and have been found to increase in the lung tissue of COVID-19 patients.

NETs are bonds consisting of chromatin, pathogenicidal proteins, and oxidant enzymes secreted by neutrophils to fight infection. However, studies prove that NETs can have adverse effects such as increased inflammation and thrombosis if not regulated properly. In inflamed tissue, neutrophils and platelets can induce immunothrombosis, forming a fibrin filter that functions to capture pathogens.[18] NETs secreted by neutrophils into the intravascular can also cause microvascular obstruction without fibrin which can lead to the death of vascularized tissue cells.[19]

Immune defense by neutrophils can cause a variety of other damages. Metalloproteases, myeloperoxidase, and ROS secreted by neutrophils are also known to damage the glycocalyx that protects endothelial cells from exposure to intravascular circulating cells. [20] Damage to the glycocalyx facilitates neutrophil adhesion to the endothelium, leading to an increase in intercellular adhesion molecule 1 (ICAM-1). Increased ICAM-1 increases transendothelial permeability through caveolae. [21] Excessive neutrophil secretory activity such as secretion of neutrophil granule contents (neutrophil elastase and defensin), ROS, NET, and inflammatory mediators such as TNF-α are known to cause increased permeability of the endothelium through damage to the glycocalyx and intercellular bonds. [22] Together with increased microvascular thrombus formation, increased vascular permeability in COVID-19 due to increased neutrophil number and activity leads to organ damage and mortality (Figure 1). This explains the association of high neutrophil levels which was found to be significantly associated with time to death in this study.

In contrast to neutrophils, findings regarding lymphocytes in this study did not show significant differences in lymphocyte levels and time to death, although lymphocyte levels in patients with time to death <48 hours were lower than >48 hours. Categorical analysis dividing subject data into lymphopenia and normal also showed no significant differences. However, lymphocyte levels were found to be significantly higher in patients with comorbidities and time to death >48 hours compared to time to death <48 hours. These findings are in accordance with the study of Illg *et al.*, which analyzed lymphocytes in 311 COVID-19 patients. In this study, no significant relationship was found between lymphocytes and various variables such as age, intubation, and outcomes in the form of death. A total of 210 subjects had lymphocytes below normal, and 101 subjects had lymphocytes above normal.[23]

Previous studies by Zhang *et al.*, showed a pattern of lymphocyte decline that was consistent with the severity of COVID-19 disease. In the study with 2923 COVID-19 subjects, 70.2% showed low lymphocyte levels. In severe cases, 64.1% showed low lymphocytes; 85.0% in critical cases; and 93.5% of cases died. A pattern of gradual increase in lymphocytes was found in severe and critical cases, whereas lymphocyte levels in deceased subjects were consistently low.[24] Wang *et al.*'s study analyzed lymphocyte counts in 134 COVID-19 patients with severe symptoms. This study found a non-linear relationship between lymphocyte levels and the risk of death. COVID-19 patients with lymphocyte counts <0.95×109/L showed a significantly increased risk of death (seven-fold) compared to patients with lymphocyte counts >0.95×109/L. This shows the potential of lymphocytes as a predictor of death in COVID-19.[5]

The findings of NLR levels in this study are different from studies that have been conducted previously. In this study, NLR was not significantly associated with time to death in general, but was significantly associated with time to death in patients with comorbidities. The study of Toori *et al.* showed a significant association of NLR with COVID-19 disease severity.[3] Liu *et al.*'s study showed an increase in mortality risk of 8% for every 1 unit increase in NLR.[4] These studies demonstrate the potential of NLR as an easy and inexpensive predictor, as well as a risk factor, of mortality in COVID-19. The relationship between NLR and time to death in this study was almost significant ($p = 0.05$), indicating a possible association of the findings with study weaknesses such as small sample size and non-multicenter study. However, the finding of a significant relationship between NLR and time to death in patients with comorbidities shows the importance of patient comorbidities in changing the composition of leukocyte differentiation in COVID-19 patients.

In this study, significant differences in lymphocyte levels and NLR based on time of death were only found in patients with comorbidities. Various COVID-19 comorbidities stated by the CDC are known to be associated with a decrease in lymphocytes and an increase in neutrophils. The systemic stress response is known to increase catecholamines and cortisol which leads to changes in leukocyte differentiation. Leukocyte differentiation in this condition leads to a lower percentage of lymphocytes. This can occur due to

regulation of lymphocyte proliferation, increased lymphocyte apoptosis, and changes in lymphocyte distribution.[25]

This study has several weaknesses. First, the study only included one health facility center as a data source, namely Dr. Saiful Anwar Malang. Second, the number of research samples was only 300 patients. Third, time of death data was collected which was only based on the time of hospital admission, so it could not represent the patient's condition before entering the hospital, and the time of death was only divided by a time limit of 48 hours. It is hoped that more time-to-death divisions will provide a more detailed analysis of the time-to-death with lymphocytes and neutrophils of COVID-19 patients.

CONCLUSION

Based on this study, it can be concluded that there is a significant relationship between neutrophil levels and time to death in COVID-19 patients, both with and without comorbidities. In addition, a significant relationship was found between lymphocyte levels and NLR and time to death in COVID-19 patients with comorbidities.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 13–19

OPEN ACCESS

Original Article

Differences of Dyspareunia in Primipara with 2nd Degree Perineal Laceration Sutured with Rapide Polyglactin 910 and Chromic Catgut Threads

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Abstract

Background : Dyspareunia is persistent or recurrent pain during sexual intercourse. Perineal laceration, spontaneous or episiotomy, is one of the most common causes. Perineal lacerations that occur must be treated through suturing. Chromic catgut is a natural thread that is often used in medical practice, but this thread have a higher inflammatory response compared to Rapide Polyglactin 910. The purpose of this study was to analyze the difference in the incidence of dyspareunia in primipara with 2nd degree perineal lacerations sutured with Rapide Polyglactin 910 and Chromic catgut threads

Methods : True experimental research with randomized controlled trial-single blinded method. The research was conducted at dr. Kariadi Semarang, RA Kartini Hospital and dr. Soeselo from August 2022 to February 2023. The research subjects were primipara with 2nd degree perineal lacerations which were divided into 2 groups, namely 45 subjects in the Chromic catgut group and 45 subjects in the Rapide Polyglactin 910 group. Evaluation of dyspareunia after 3 months was carried out using the Female Sexual Function Index (FSFI)

Results : Subjects sutured using Chromic catgut had a 2.7 times greater risk of experiencing dyspareunia when compared to using Rapide Polyglactin 910 (OR=2.7; 95% CI=1.1–6.6). A significant confounding factor was found, namely the act of episiotomy (p=0.047; OR=9.56; 95% CI=1.86–48.97). After controlling for these variables, the subjects who were sewn using Chromic had a significant risk (p=0.002, OR=5.39; 95% CI=1.76–16.50)

Conclusion : Subjects with Chromic catgut have a higher risk of experiencing dyspareunia than using Rapide Polyglactin 910 threads after 3 months of suturing.

Keywords : dyspareunia; chromic catgut; rapide polyglactin 910; perineal laceration, FSFI

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.968

Accepted: May 30th, 2023
Approved: December 18th, 2023

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INTRODUCTION

Dyspareunia is persistent or recurrent pain during sexual intercourse. Ten to twenty percent of women will experience dyspareunia for any reason.[1] It often occurs in postpartum women and is suspected to occur due to anatomical and hormonal changes.[2,3] Postpartum women experience sexual dysfunction as much as 69% and 17–36% of them experience dyspareunia.[4–7] The most common risk factors for dyspareunia after delivery are perineal and genital trauma and episiotomy.[7–9]

Perineal laceration is the most common occurrence. This can be caused by a spontaneous tear or an episiotomy. At delivery, 66% of women experience perineal lacerations.[10] Perineal lacerations, whether arising spontaneously or because of an episiotomy, must be repaired with the best possible surgical technique and with the ideal thread.

Chromic Catgut is a natural thread that is often used in medical practice in developing countries, including in Indonesia. The use of natural threads can cause a more severe tissue reaction compared to synthetic threads. Postpartum patients who are sutured with Chromic Catgut have 3.9 times the risk of experiencing dehiscence compared to using synthetic threads.[11] The dehiscence that occurs is influenced by various factors, including inflammation and infection that occurs in the suturing area. Inflammatory conditions and infections in the suturing area can cause dyspareunia. Dyspareunia occurs more frequently in women with perineal lacerations who are sutured with Chromic Catgut.[12]

Rapide Polyglactin 910 is a synthetic material thread which can also be used for repair of perineal lacerations to prevent prolonged morbidity. Research shows that there are significant differences regarding the repair of perineal lacerations, both in wound healing and the incidence of dyspareunia.

This study aims to determine differences in the incidence of dyspareunia in patients after perineal suturing with Chromic Catgut and Rapide Polyglactin 910 threads which are focused on evaluating 3 months postpartum.

METHODS

True experimental research with randomized controlled trial-single blind method. The research was conducted at dr. Kariadi Semarang, RA Kartini Hospital and dr. Soeselo for 6 months from June 2022 to November 2022. The research subjects were primiparas with grade 2 perineal lacerations who met the inclusion criteria and did not have exclusion criteria. The study inclusion criteria included: 1) primiparous, 2) normal sexual intercourse before pregnancy (FSFI score ≥ 36), 3) vaginal delivery and perineal laceration degree 2 either spontaneously or with an episiotomy, and 4) willing to participate in the study and sign informed consent. The study exclusion criteria included: 1) perineal infection before suturing, 2) previous perineal injury, 3) perineal wound > 24 hours, 4) device delivery, 5) positive Cotton Swab Test, 6) post-perineal suturing 24 hours. Based on the calculation of the sample using the 2-group comparison formula using p2 = 0.32 and RR 1.85 from previous studies, it was found that there were 45 subjects in each group with a total of 90 subjects. Evaluation of dyspareunia after 3 months was carried out using the Female Sexual Function Index (FSFI) questionnaire question number 19. If a score is obtained with a value of 5 then it is said that there is no dyspareunia, but if a value <5 is obtained then it is said that dyspareunia has occurred.

Figure 1. Types of suture threads. (a) Rapide Polyglactin 910, (b) Chromic catgut

RESULTS

Obstetric and gynecological status assessments performed between the Chromic and Rapide Polyglactin 910 groups showed that there were significant differences in episiotomy procedures (p=0.050), where there were more episiotomies performed in the Rapide Polyglactin 910 group than the Chromic group (Table 1).

The FSFI assessment conducted between the Chromic and Rapide Polyglactin 910 groups showed no significant difference in the interveal between the first postpartum sexual day (p=0.315), total FSFI score (p=0.292), volitional FSFI score (p=0.855), arousal FSFI score (p=0.351), lubrication FSFI score (p=0.196), climax FSFI score (p=0.501), satisfaction FSFI score (p=0.702) and dyspareunia FSFI score (p=0.139) (Table 2).

TABLE 1
Characteristics of research subjects

Characteristics		Thread Type				*p**
		Chromic (n=45)		>48 hours (N=176)		
		n	Mean (SD); Median (min–max)	n	Mean (SD); Median (min–max)	
Age			23.82 (4.14); 24 (17–35)		24.24 (3.94); 24 (15–32)	0.382‡
Education Level	Junior High School	18 (40)		12 (27)		0.404§
	Senior High School	23 (51)		28 (62)		
	Bachelor	4 (9)		5 (11)		
Diabetes mellitus	No	42 (93)		41 (91)		1.000§
	Yes	3 (7)		4 (9)		
Antibiotic	No	20 (44)		24 (53)		0.527¥
	Yes	25 (56)		21 (47)		
Birth weight	≤4000 grams	45 (100)	2882.11 (536.93); 3000 (1300–3900)	45 (100)	2955.89 (498.57); 2965 (1100–3900)	0.765‡
	>4000 grams	0 (0)		0 (0)		
Long phase 2	<2 hour	45 (100)	24.80 (13.79); 20 (5–60)	45 (100)	23.07 (12.74); 20 (5–60)	0.596‡
	≥2 hour	0 (0)		0 (0)		
Episiotomy	No	9 (20)		2 (9)		0.050¥
	Yes	36 (80)		43 (91)		

‡Mann Whitney U; ¥Chi-square; §Fischer exact; significant $p \leq 0.05$

TABLE 2
Female Sexual Function Index

		Thread Type				*p*
		Chromic (n=45)		Rapide Polyglactin 910 (n=45)		
		n	Mean (SD); Median (min–max)	n	Mean (SD); Median (min–max)	
First sexual intercourse after childbirth	<3 months	38 (84)	51.56 (17.83); 60 (30–90)	42 (93)	53.33 (20.11); 60 (30–90)	0.315¥
	≥3 months	7 (16)		3 (7)		
FSFI Total	No sexual dysfunction	4 (9)	25.99 (2.65); 25.9 (20.3–30.6)	25 (55)	26.05 (4.04); 27.1 (18.9–39)	0.292¥
	Sexual dysfunction	42 (93)		20 (45)		

TABLE 2. Continued.

	Thread Type				*p*
	Chromic (n=45)		Rapide Polyglactin 910 (n=45)		
	n	Mean (SD); Median (min–max)	n	Mean (SD); Median (min–max)	
FSFI (Desire)	–	3.96 (0.61); 4.2 (2.4–4.8)	–	3.92 (0.95); 4.2 (1.2–5.4)	0.855‡
FSFI (Arousal)	–	4.22 (0.44); 4.2 (3–5.1)	–	4.11 (0.62); 4.2 (2.4–5.4)	0.351‡
FSFI (Lubrication)	–	4.76 (0.69); 4.8 (2.1–6.0)	–	4.48 (0.98); 4.5 (0–5.7)	0.196‡
FSFI (Climax)	–	4.27 (0.73); 4.4 (2.4–5.6)	–	4.42 (0.62); 4.4 (3.2–5.6)	0.501‡
FSFI (Satisfaction)	–	4.34 (0.82); 4.8 (2.4–6.0)	–	4.26 (0.82); 4.8 (2.4–5.8)	0.702‡
FSFI (Dyspareunia)	–	4.39 (0.83); 4.4 (2.8–6.0)	–	4.64 (0.82); 4.8 (2.8–6.0)	0.139‡

†Independent T test; ‡Mann Whitney U; ¥Chi-square; §Fischer exact; significant $p \leq 0.05$

TABLE 3
The incidence of dyspareunia based on the type of thread

Dyspareunia	Thread Type		*p*	OR (CI 95%)
	Chromic (n=45)	Rapide Polyglactin 910 (n=45)		
Yes	34 (75.6%)	24 (53.3%)	0.047¥	2.70 (1.10–6.63)
No	11 (24.4%)	21 (47.7%)		

¥Chi-square; significant $p \leq 0.05$

TABLE 4
Factors influencing dyspareunia

Dyspareunia	*p*	OR (95% CI)
Thread Type	0.004	5.515 (1.712 – 17.764)
Age	0.429	1.053 (0.926 – 1.199)
Education	0.658	1.234 (0.487 – 3.131)
Episiotomy	0.007	9.564 (1.867 – 48.977)
First sexual intercourse after childbirth	0.404	0.509 (0.104 – 2.492)
Long phase II	0.403	0.983 (0.944 – 1.023)
Birth weight	0.570	1.000 (0.999 – 1.001)
Diabetes mellitus	0.298	0.392 (0.067 – 2.289)
Antibiotics	0.657	1.260 (0.455 – 3.493)

£Logistic regression; significant $p<0.05$

TABLE 5
The incidence of dyspareunia based on the type of thread after controlling the episiotomy subject

Dyspareunia on episiotomy	Thread Type		*p*	OR (CI 95%)
	Chromic (n=36)	Rapide Polyglactin 910 (n=43)		
Yes	31 (86.1%)	23 (53.5%)	0.002¥	5.39 (1.76–16.50)
No	5 (13.9%)	20 (46.5%)		

¥Chi-square; significant $p \leq 0.05$

TABLE 6
Factors influencing dyspareunia after episiotomy control subjects

Dyspareunia	*p*	OR (95% CI)
Thread Type	0.002	7.56 (2.06 – 27.66)
Age	0.944	1.00 (0.86 – 1.16)
Education	0.337	1.65 (0.59 – 4.63)
First sexual intercourse after childbirth	0.652	0.67 (0.12 – 3.76)
Long time II	0.422	0.98 (0.94 – 1.02)
Birth weight	0.255	0.99 (0.99 – 1.00)
Diabetes mellitus	0.299	0.37 (0.61 – 2.36)
Antibiotics	0.625	1.32 (0.43 – 4.06)

£ Logistic regression; significant $p<0.05$

The results of calculating the OR value proved that subjects sutured using Chromic had a 2.7 times greater risk of experiencing dyspareunia when compared to subjects sutured using Rapide Polyglactin 910 (OR=2.7; 95% CI=1.1-6.6; p=0.047) (Table 3).

Based on the multivariate test using logistic regression, a relationship was found between the incidence of dyspareunia and the type of suture thread (p=0.004) and episiotomy (p=0.007). Patients who are sutured using Chromic thread have a 5.51x higher risk of experiencing dyspareunia. Patients who undergo episiotomy have a 9.56x higher risk of experiencing dyspareunia (Table 4).

Further analysis was carried out by controlling the episiotomy variable so that it was able to show a direct relationship between the use of the type of thread and the incidence of dyspareunia.

After controlling the episiotomy subject, the results of calculating the OR value proved that subjects sutured using Chromic had a 5.39 times greater risk of experiencing dyspareunia when compared to subjects sutured using Rapide Polyglactin 910 (OR=5.39; 95% CI=1.76-16.50; p=0.002) (Table 5).

Based on the multivariate test using logistic regression, a relationship was found between the incidence of dyspareunia and the type of suture thread (p=0.002). Patients who are sutured using Chromic thread have a 7.56x higher risk of experiencing dyspareunia (Table 6).

DISCUSSION

Evaluations carried out on 90 sexually active research subjects showed that the total FSFI score at the end of the study between the two study groups did not show a significant difference. Based on the analysis of the incidence of dyspareunia, there was a significant difference between the two study groups.

The FSFI questionnaire consists of several assessment components, namely volition, arousal, lubrication, climax, satisfaction, and dyspareunia. This shows that it is not only the condition of dyspareunia that plays a major role in the incidence of sexual dysfunction, but there are 5 other components that play a role. In this study, the median FSFI score for lubrication was higher in the Chromic group, the median FSFI score for dyspareunia was higher in the Rapid Polyglactin 910 group, but the median FSFI score for volition, arousal, climax, and satisfaction was similar between the two groups. Most of the final FSFI scores were similar

between the two study groups, meaning that there was no significant difference in the total final FSFI scores.

The final FSFI score for dyspareunia between the two study groups did not show a significant difference, but the incidence of dyspareunia showed a significant difference between the two study groups.

Patients who are sutured with Chromic sutures or undergo episiotomy are at high risk for dyspareunia. After controlling for the episiotomy variable, a relationship was still found between the use of Chromic threads and the risk of dyspareunia.

There is a difference in the tensile strength between Chromic and Rapide Polyglactin 910 threads. Chromic threads are known to have a tensile strength of 17–21 days while Rapide Polyglactin 910 threads have a tensile strength of 10–14 days. The use of Chromic threads has an absorption capacity of up to 90–100 days, while Rapide Polyglactin 910 threads have a faster absorption rate of 42 days.[13–15] The use of Rapide Polyglactin 910 threads can be absorbed naturally thereby reducing pain compared to the use of Chromic threads. This difference causes Chromic threads to have the ability to bond between networks longer and the absorption capacity of threads lasts longer. Even so, the use of Rapide Polyglactin 910 threads still causes dyspareunia. A study conducted in the Netherlands in 2017 found that 52–59% and 20–32% of patients still complained of symptoms of dyspareunia after 6 weeks and 3 months of suturing using Rapide Polyglactin 910 thread.[16] These results are supported by previous studies where 34–67% of women have not continued sexual intercourse at 6–7 weeks and 2–12% at 3 months after episiotomy or grade 2 perineal rupture due to dyspareunia.[17,18] A study in the Czech Republic found that after 3 months 49% of subjects complained of dyspareunia, and after 6 months 32% each complained of dyspareunia.

A study in Jogjakarta in 2021 assessing pain and wound repair found that a significant reduction in pain occurred on the 10th day for the Rapide Polyglactin 910 group and the 12th day for the Chromic group. Another study also stated that the complications of dyspareunia in the first 6 weeks in the group using Chromic threads were 86% and decreased to 12% after 3 months. Whereas in the use of Rapide Polyglactin 910 the incidence of dyspareunia was 8% in the first 6 weeks after suturing the perineal wound and after 3 months of observation there were no subjects complaining of dyspareunia. It can be concluded that the use of Rapide Polyglactin 910 thread has better absorption and better wound healing so that complications of dyspareunia are smaller than the use of Chromic thread.[14] In line with the results of this study, it was stated that the use of Rapide Polyglactin 910 thread is an ideal suture thread for perineal laceration repair which results in better wound healing compared to the use of Chromic thread.

Chromic threads are produced from collagen originating from the intestines of animals (sheep and cattle) and are reported to cause an inflammatory response in tissues because the threads are broken down by proteolytic enzymes and phagocytosis. Collagen is a very unstable and unpredictable substance in terms of how long it takes to be absorbed, especially if there is a wound infection or malnutrition. Rapide Polyglactin 910 yarn, composed of glycolide and lactide copolymers with a ratio of 90/10 and the substance is derived from glycolic and lactic acids. The material is stranded on top of each other for easier handling and coated with a 65/35 ratio copolymer blend of glycolide and lactide and the same ratio of calcium stearate to reduce bacterial attachment and excess traction on tissues. This is consistent with the results of a study which stated that Rapide Polyglactin 910 thread was preferred over Chromic thread because of its non-allergic nature (inflammatory response) and lower risk of complications of infection and removal of stitches.[14] For this reason, there was a difference in the incidence of dyspareunia between the use of Chromic and Rapide Polyglactin 910 threads.

Episiotomy is also known to trigger dyspareunia. Episiotomy is a perineal surgical incision to speed up and simplify the delivery process by enlarging the birth canal.[19] The most common type of episiotomy is performed mediolaterally (from the hymenal ring downwards at a 45-degree angle).[20] Several anatomical structures will be cut in a mediolateral episiotomy including the vaginal epithelium, transverse perineal muscles, bulbocavernosus muscles, and perineal skin. A mediolateral episiotomy that is too deep or too wide can expose the ischiorectal fossa. The mediolateral incision is known to pose a greater risk of injury to the ipsilateral nerve, muscle, erectile, and glandular tissue.[21] Therefore it is not surprising that an episiotomy can trigger dyspareunia due to damage to several structures in the perineal area.

CONCLUSION

There is a significant difference in the incidence of dyspareunia in primiparas with 2nd degree perineal lacerations sewn with Rapide Polyglactin 910 and Chromic Catgut threads, where subjects using Chromic threads have a greater risk of dyspareunia than subjects using Rapide Polyglactin 910 threads.

Funding

This research did not receive a specific grant from a funding agency in the public, commercial, or not-for-profit sector.

Conflict of Interest

The authors clarify that they have no competing financial interests or personal relationships that could influence the work reported in this paper.

Research Ethics

The research was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University – dr. Kariadi Hospital and carried out in accordance with the principles of the Declaration of Helsinki.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 20–25

OPEN ACCESS

Original Article

Pregnancy Associated Plasma Protein-A (PAPP-A) as a Marker to Distinguish Normotensive with Early 2nd Trimester and Late 3rd Trimester Onset of Preeclampsia

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Abstract

Background : Preeclampsia is a hypertensive condition that occurs after 20 weeks of gestation accompanied by target organ damage. Complications of preeclampsia can cause intrauterine fetal growth retardation, and placental hypoperfusion, even in the most serious situations, namely termination of pregnancy and death of the fetus and/or mother. Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight glycoprotein that is produced in the placenta and secreted into the maternal bloodstream. However, based on several studies that have been conducted, there is uncertainty in the results of assessing PAPP-A levels obtained in pregnant women in the second and third trimesters. The aims of this study was to proving differences in PAPP-A levels in the second and third trimesters in the incidence of early-onset preeclampsia and normotensive pregnancy.

Methods : An analytic observational study with a cross-sectional approach was carried out in the delivery room of RSUP Dr. Kariadi Semarang, Halmahera Health Center, Ngesrep Health Center, Bulu Health Center, and private midwife practice in Semarang City. The subjects of the study were six 2nd-trimester preeclampsia patients, fourteen 3rd-trimester preeclampsia patients, and twenty normotensive pregnancy patients who met the inclusion and exclusion criteria. Data were analyzed using Mann Whitney with a significance of $p<0.05$

Results : There was a significant difference in PAPP-A levels ($p<0.001$) between the preeclampsia and normotensive pregnancy groups, whereas PAPP-A levels were higher in the preeclampsia group. There were significant differences in PAPP-A levels ($p<0.001$) between the 2nd-trimester preeclampsia, 3rd-trimester preeclampsia, and normotensive pregnancies, where the highest PAPP-A levels were found in the 2nd-trimester preeclampsia group.

Conclusion : There was a significant difference in PAPP-A levels between the second and third trimesters of early-onset preeclampsia compared to normotensive pregnancies, where PAPP-A levels were higher in the second and third trimesters of early-onset preeclampsia. Elevated PAPP-A levels in the second and third trimesters are associated with an increased risk of early-onset preeclampsia.

Keywords : PAPP-A, Early Onset Preeclampsia, Normotensive Pregnancy, Second Trimester, Third Trimester

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.979

Accepted: June 20th, 2023
Approved: December 19th, 2023

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INTRODUCTION

Preeclampsia is a multi-systemic syndrome involving genetic and environmental factors in its pathogenesis. Preeclampsia is divided into two types based on the time of occurrence, early-onset and late-onset preeclampsia.[2] According to the American College of Obstetrics and Gynecology (ACOG), preeclampsia is a condition of hypertension and proteinuria that occurs after 20 weeks of gestation in patients who were previously normotensive. As the understanding of preeclampsia as a heterogeneous hypertensive disorder of pregnancy develops, ACOG's Hypertension 2013 revised the definition of preeclampsia to include worsening of symptoms with or without proteinuria and to exclude the degree of proteinuria as a criterion of worsening symptoms.[2]

Preeclampsia is divided into two types based on the time of occurrence, early onset, and late-onset preeclampsia. The main pathology of early-onset preeclampsia is incomplete spiral artery transformation, resulting in placental hypoperfusion and reduced nutritional supply to the fetus causing signs of fetal growth restriction (FGR). Complications arising from preeclampsia can cause intrauterine fetal growth retardation, and placental hypoperfusion, even in the most serious situations, namely termination of pregnancy and death of the fetus and/or mother.[1,2]

Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight glycoprotein that is produced in the placenta and secreted into the maternal bloodstream. Placental pathology is believed to reduce PAPP-A levels. The etiology of preeclampsia is unknown, but several potential etiologies include abnormal trophoblastic invasion of the uterine vessels and immunological intolerance between fetoplacental and maternal tissues. At 11–14 weeks of gestation, PAPP-A levels decrease which then develops into preeclampsia. Pathological processes leading to low maternal serum levels include decreased trophoblast mass and function, and abnormal placental circulation. Maternal serum concentrations of PAPP-A increase soon after the appearance of preeclampsia and increase slightly at 22+0 24+6 weeks of gestation. In women with preeclampsia in the third trimester, levels increase. Elevated serum PAPP-A was reported soon after the onset of preeclampsia with leakage from damaged villous cells and injury to chorionic villus cells. During gestation, most of PAPP-A is synthesized in the placental syncytiotrophoblast, and serum concentrations increase from pregnancy to term.[3]

However, based on several studies that have been conducted, there is uncertainty in the results of assessing PAPP-A levels obtained in pregnant women in the second and third trimesters. The results of the study found that PAPP-A levels tended to be higher in the second and third trimesters.[4] It has been mentioned that there is an increase in PAPP-A levels of up to 20% in the second and third trimesters.[5] However, other studies stated different things, that PAPP-A levels decreased during the first trimester and the value did not differ significantly in the second trimester.[6] At the beginning of the second trimester, PAPP-A levels of women who will experience preeclampsia decrease to 1/3 lower than women who do not experience preeclampsia.[7]

This study aims to prove the difference in PAPP-A levels in the second and third trimesters in the incidence of early-onset preeclampsia and normotensive pregnancy.

METHODS

The research has received ethical permission from KEPK with No. 1453/EC/KEPK-RSDK/2023. An analytic observational study with a cross-sectional approach that was carried out in the delivery room of RSUP Dr. Kariadi Semarang, Halmahera Health Center, Ngesrep Health Center, Bulu Health Center, and private midwife practice in Semarang City. The subjects of the study were 20 early onset preeclampsia patients and 20 normotensive pregnancy patients who met the inclusion and exclusion criteria. The inclusion criteria were: 1) Willing to become research subjects, 2) Pregnant women aged 20–35 years, 3) Primigravida and multigravidas, 4) Preeclampsia with early onset of gestational age <34 weeks, 5) Pregnancy with an intrauterine single fetus. Exclusion criteria were: 1) Unclear first day of last menstrual period (HPHT), 2) History of preeclampsia, 3) Pregnant women with chronic diseases, including diabetes mellitus, cerebrovascular disease, chronic hypertension, chronic kidney failure, and chronic infection. Data were analyzed using SPSS statistics application with a significance of $p<0.05$.

RESULTS

Age, in the preeclampsia group, was found to be an average of 29.9 years with a standard deviation of 6.43 years. In the normotensive group, the mean was 29.35 years with a standard deviation of 4.51 years. There was no significant difference in the age distribution ($p=0.756$) between the preeclampsia and normotensive groups.

Body mass index, in the preeclampsia group, obtained a median value was 28.85 kg/m^2 with the smallest value being 24.8 kg/m^2 and the largest value being 29.7 kg/m^2. In the normotensive group, the median value was 25.7 kg/m^2 with the smallest value being 19 kg/m^2 and the largest value being 29.7 kg/m^2. There was a significant difference in the distribution of body mass index ($p=0.005$) between the preeclampsia and normotensive groups, where a higher body mass index was found in the preeclampsia group (Table 1).

TABLE 1
Characteristics of respondents

Variable	Preeclampsia (n=20)	Normotensive (n=20)	*p*
Age (years)	29.90 ± 6.43	29.35 ± 4.51	0.756†
Body mass index	28.85 (24.8–29.7)	25.7 (19–29.7)	0.005‡

†Independent T-test; ‡Mann Whitney U; *significant *p*<0.05

TABLE 2
PAPP-A levels in cases of preeclampsia

Variable	Preeclampsia Mean ± SD; Median (min–max)	Normotensive Mean ± SD; Median (min–max)	*p*
PAPP-A Level	3.17 (0.63–43.72)	0.67 (0.24–3.01)	<0.001

Mann Whitney U; *significance *p*<0.05

TABLE 3
PAPP-A levels in cases of 2nd-trimester preeclampsia, 3rd-trimester preeclampsia and normotensive pregnancy

Variable	Preeclampsia TM2 Mean ± SD; Median (min–max)	Preeclampsia TM3 Mean ± SD; Median (min–max)	Normotensive Mean ± SD; Median (min–max)	*p*
PAPP-A Level	3.75 (2.38–15.18)	2.3 (0.63–43.72)	0.67 (0.24–3.01)	<0.001

Kruskal Wallis; significant *p*<0.05

TABLE 4
The risk of preeclampsia based on PAPP-A levels

Variable		Preeclampsia		*p*	PR (95% CI)
		Preeclampsia	Normotensive		
Rate PAPP-A	≥1.61 ng/mL	16	5	0.001	3.61 (1.46–8.92)
	<1.61 ng/mL	4	15		

Chi-Square; significant *p*<0.05

PAPP-A levels, in the preeclampsia group, obtained a median value was 3.17 ng/mL with the smallest value being 0.63 ng/mL and the largest value being 43.72 ng /mL. In the normotensive group, the median value was 0.67 ng/mL with the smallest value being 0.24 ng/mL and the largest value being 3.01 ng/mL. There was a significant difference in PAPP-A levels (p<0.001) between the preeclampsia and normotensive groups, where PAPP-A levels were higher in the preeclampsia group (Table 2).

PAPP-A levels, in the 2nd-trimester preeclampsia group, obtained a median value was 3.75 ng/mL with the smallest value being 2.38 ng/mL and the largest value being 15, 18ng/mL. In the 3rd-trimester preeclampsia group, the median value was 2.3 ng/mL with the smallest value being 0.63 ng/mL, and the largest value was 43.72 ng/mL. In the normotensive group, the median value was 0.67 ng/mL with the smallest value being 0.24 ng/mL and the largest value being 3.01 ng/mL. There were significant differences in PAPP-A levels (p<0.001) between the 2nd-trimester preeclampsia, 3rd-trimester preeclampsia, and normotensive pregnancies, where the highest PAPP-A levels were found in the 2nd-trimester preeclampsia group (Table 3).

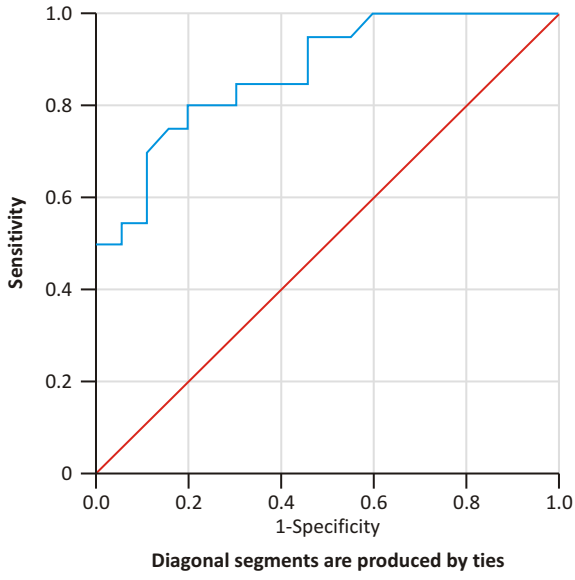

Figure 1. TROC curve of PAPP-A levels on the incidence of preeclampsia.

Based on ROC analysis and AUC curve, it was found that PAPP-A levels (p<0.001; AUC=0.878) were related to the incidence of preeclampsia. PAPP-A levels with a cut off 1.61 ng/mL have a sensitivity of 80% and specificity of 80% (Figure 1).

In subjects with PAPP-A levels >1.61 ng/mL, 16 subjects had preeclampsia and 5 subjects without preeclampsia. In subjects with PAPP-A levels <1.61 ng/mL, there were 4 subjects with preeclampsia and 15 subjects without preeclampsia (Table 4).

There is a relationship between PAPP-A levels and the incidence of preeclampsia (p=0.001). Individuals with PAPP-A levels > 1.61 ng/mL have a 3.61x (PR 3.61; 95% CI 1.46–8.92) greater risk of experiencing preeclampsia than individuals with PAPP-A levels < 1.61 ng/mL.

DISCUSSION

The research subjects were dominated by women aged 29–30 years. In the preeclampsia group, the body weight and body mass index status were significantly higher than in the normotensive group.

Janani F, *et al* who researched cases of preeclampsia found that the average age of patients with preeclampsia was 28.6 years.[8] Tabassum S, *et al* who assessed maternal and perinatal clinical outcomes in patients with preeclampsia also reported that the mean age of patients with preeclampsia was 32.27 years with a body mass index of 33.19 kg/m^2.[9] Arwan B, *et al* in his research stated that patients who tend to preeclampsia are patients with overweight and obese BMI status with a high-risk age range.[10] Excessive weight gain during pregnancy will increase the risk three times greater for preeclampsia.[11] This study shows that there is a relationship between BMI and the incidence of preeclampsia. Motedayen M, *et al* in a systematic research review and meta-analysis regarding the relationship between body mass index and the incidence of preeclampsia reported that there was a significant relationship between BMI and the risk of preeclampsia.[12] In pregnant women who are overweight, preeclampsia can occur through the mechanism of hyperleptinemia, metabolic syndrome, inflammatory reactions and increased oxidative stress which lead to endothelial damage and dysfunction.[13]

In this study, there was a significant difference in PAPP-A levels between the preeclampsia and normotensive groups, where PAPP-A levels were higher in the preeclampsia group. There is a correlation between PAPP-A levels and the incidence of preeclampsia, where increased PAPP-A levels are associated with an increased incidence of early-onset preeclampsia with a moderate positive correlation level. Individuals with PAPP-A levels >1.61 ng/mL have a 3.61x greater risk of experiencing preeclampsia than individuals with PAPP-A levels <1.61 ng/mL.

PAPP-A is a marker used to show perfusion function and vascular resistance. During pregnancy, PAPP-A protein is synthesized primarily by syncytiotrophoblast cells and septal X cells derived from trophoblasts in placental tissue. At concentrations 100–1000 fold lower than those obtained during the first trimester of pregnancy, PAPP-A protein is also expressed in other reproductive tissues (ovaries, uterine tubes, endometrium and myometrium, and prostate in males), in female and non-reproductive tissues. male (kidney,

colon, bone marrow cells, and breast), and in pathophysiologically modified tissues (eg breast and prostate cancers). [14]

Preeclampsia is associated with increased PAPP-A; the highest values are recorded before the obvious manifestations of preeclampsia. Elevated PAPP-A levels occur up to 1.5-fold compared with healthy pregnancies and are observed in both mild and severe preeclampsia, with no difference between mild and severe cases.[15] In addition, PAPP-A is correlated with mean arterial blood pressure. In a recent study, PAPP-A was measured at 30–33 weeks' gestation as a screening method for preeclampsia that developed after 34 weeks and did not differ significantly from controls. Some studies have shown that PAPP-A levels are increased in preeclampsia.[16] A study by Wright and colleagues showed that PAPP-A serum levels increased in pregnant women with above average body weight, in pregnant women from the Afro-Caribbean, South Asian and East Asian races against pregnant women. Caucasian race. Meanwhile, PAPP-A serum levels decreased in pregnant women with above average height, pregnant women who were smokers, and multiparous pregnant women with or without a previous history of preeclampsia compared to nulliparous pregnant women.[5] These factors are thought to have caused a significant increase in PAPP-A levels in this study and led to differences in PAPP-A results with previous studies.

In this study, the highest PAPP-A levels were significantly found in 2nd-trimester preeclamptic subjects, while the lowest PAPP-A levels were found in normotensive subjects.

Research conducted by Spencer K, *et al* found that there was an increase in PAPP-A levels in pregnant women with preeclampsia at 22–24 weeks gestation.[17] Uriel M, *et al* in his research found that PAPP-A levels in first-trimester preeclampsia subjects had a greater value than normal pregnancy subjects.[18]

Multivariate analysis showed that together, there was a relationship between body weight and PAPP-A levels on the incidence of preeclampsia. PAPP-A levels have a stronger relationship to the incidence of preeclampsia than body weight.

Various studies have confirmed that obesity in mothers increases the risk of preeclampsia by 3–4x higher when compared to mothers with normal weight.[19] A cohort study conducted in Lanzou, China supports the hypothesis that weight gain during pregnancy increases the risk of obesity and that pre-pregnancy obesity and gestational weight gain increase the risk of pre-eclampsia, both independently and together, as a combined effect of maternal and maternal obesity. gestational weight gain further increases the risk of pre-eclampsia.[20]

The advantage of this study is that it can show dynamic changes in PAPP-A levels along the trimesters of pregnancy in patients with preeclampsia which is able to show a decrease in values as gestational age increases. The limitation of this study is that the incidence of preeclampsia is not only influenced by PAPP-A levels but also by the body mass index of the study subjects. Future research should control the subject's body mass index to eliminate confounding variables.

CONCLUSION

There was a significant difference in PAPP-A levels between the second and third trimesters of early-onset preeclampsia compared to normotensive pregnancies, where PAPP-A levels were higher in the second and third trimesters of early-onset preeclampsia. Elevated PAPP-A levels in the second and third trimesters are associated with an increased risk of early-onset preeclampsia. Individuals with PAPP-A levels in the second and third trimesters >1.61 ng/mL have a 3.61x (PR 3.61; 95% CI 1.46–8.92) greater risk of experiencing preeclampsia than individuals with PAPP-A levels trimester II and III <1.61 ng/mL

Funding

This research did not receive a specific grant from a funding agency in the public, commercial, or not-for-profit sector.

Conflict of Interest

The authors certify that they have no competing financial interests or personal relationships that could influence the work reported in this paper

Research Ethics

The research was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University Dr. Kariadi and carried out following the principles of the Declaration of Helsinki.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 26–32

OPEN ACCESS

Original Article

Comparison Between Placenta Accreta Index and Tovbin Score as A Predictor of Placenta Accreta Spectrum Disorders (PASD)

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.980

Accepted: July 05th, 2023
Approved: December 19th, 2023

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Abstract

Background : The incidence of Placenta Accreta Spectrum Disorders (PASD) in developed countries has reportedly increased 10-fold in the last 50 years. The significant increase was followed by an increase in the number of caesarean section from 12.5% to 23.5% in the last 10 years. Maternal morbidity related to PASD events reaches 7% in intraoperative and postoperative actions, while the morbidity reaches 60%. In cases of late diagnosis, maternal mortality with placenta accreta reaches 30%. Efforts to prevent maternal morbidity and mortality can be carried out by early detection at antenatal care visits. The Placenta Accreta Index (PAI) and Tovbin scoring systems based on the results of ultrasound examination can be used to screening for placenta accreta. The objectives of this study was to analyze the comparison of the accuracy of the PAI and Tovbin scoring systems in predicting the incidence of Placenta Accreta Spectrum Disorder (PASD).
Methods : The study used an analytic observational with a cross sectional design. Sampling was done by consecutive sampling method. There were 35 subjects who met the inclusion and exclusion criteria. PAI and Tovbin scoring were performed on each selected subject. The accuracy of the PAI and Tovbin scoring systems was confirmed by establishing a diagnosis based on PASD histopathology.
Results : The PAI scoring system in predicting PASD has a sensitivity value of 79.31%, a specificity of 83.33%, a positive predictive value (NDP) of 95.83%, a negative predictive value (NDN) of 45.45%, an accuracy of 80.00%. While the Tovbin scoring system obtained a sensitivity value of 86.21%, specificity of 83.33%, NDP of 96.15%, NDN of 55.56%, accuracy of 85.71 %.
Conclusion : In the comparison of scoring systems, it was found that the Tovbin scoring system has almost the same sensitivity and accuracy and the same specificity in predicting Placenta Accreta Spectrum Disorder (PASD).

Keywords : PAI, PASD, Placenta Accreta, Tovbin Score

INTRODUCTION

Placenta Accreta is an abnormality or abnormal invasion of the placental tissue in the underlying layer, namely the uterine muscle.[1] The degree of abnormal placental implantation can be classified into three stages, placenta accreta, increta, and percreta. These three placental attachment disorders are now better known as Placenta Accreta Spectrum Disorders (PASD). The incidence of PASD in developed countries has increased 10-fold in the last 50 years, this is associated with an increase in the number of caesarean sections. A significant increase was followed by an increase in the rate of cesarean section from 12.5% to 23.5% in the last 10 years.[1–5] The incidence of placenta accreta in cases of placenta previa varied between 1.18%,9.3 and 10% of them with anterior placenta previa The mortality rate for placenta accreta reaches 7%, both intraoperatively and due to postoperative morbidity due to massive bleeding, infection, and organ damage, uterine damage,[4,5] and some report a morbidity rate of up to 60%.[5] Various efforts to prevent increased maternal mortality and morbidity from placenta accreta have been sufficiently studied, such as the use of ultrasound examination at antenatal visits to detect placenta accreta early. The American Journal of Obstetrics and Gynecology (AJOG) has issued a scoring system called the Placenta Accreta Index (PAI) score to predict whether a pregnant woman with placenta previa also suffers from placenta accreta.[6] Diagnostic test research in 2016, they issued a new scoring system that commonly referred to as the Tovbin Score. Scoring system that has been proposed by Tobvin showed sensitivity of 86–100%, the scoring system included the number of placental lacunae and obliteration of the uteroplacental demarcation.[7] The sensitivity and specificity of various ultrasound features for PASD change across the spectrum of placental invasion, and there is significant interobserver variability in the interpretation of placental invasion. As most ultrasound features are poorly defined.[8,9] At present, there is no consensus on a diagnostic standard for PAS. Combined evaluation of multiple indicators can objectively assess risk of PAS. The "Placenta Accreta Index", "ultrasound staging system for PAS", and "two-criteria system" have good diagnostic performance for PAS; however, sample selection (placenta previa or a history of cesarean section, or both), and the varying number, selection, and assignment of scoring indicators limit their clinical application.[10–15] Accurate prenatal diagnosis of PASD is challenging, especially in less severe cases, and diagnostic criteria remain under debate. The scoring system that is often used in RSUP Dr. Kariadi Semarang is the Placenta Accreta Index (PAI) score. However, the Tovbin scoring is still rarely used in Dr. Kariadi Semarang to predict the incidence of placenta accreta. The level of accuracy of both scores in predicting the incidence of placenta accreta at RSUP Dr. Kariadi Semarang has never been studied before. Therefore, establishing the correct diagnosis of placenta accreta by a specialist in Obstetrics and Gynecology is very important so that the referral process can be carried out in a timely manner. The objective of this study was to prospectively compare two diagnostic criteria between PAI and Tovbin score, evaluate its diagnostic value, and provide a practical approach to prenatal diagnosis of PASD.

METHODS

This research is an analytic observational study with a cross sectional design conducted at Dr Kariadi General Hospital, Semarang. The study began in August 2022 – April 2023. The research subjects were patients who met the inclusion and exclusion criteria. The inclusion criteria of this study included (1) Pregnant women with suspected placenta accreta, (2) Pregnant women with placenta previa, (3) Pregnant women with a history of previous CS, (4) Pregnant women with a history of uterine surgery, (5) Pregnant women with a previous history of placenta previa, (6) Pregnant women with third trimester pregnancies, (7) Obstetrical ultrasound (Voluson E8, GE Medical Systems, Zipf, Austria) examination and placenta accreta screening were performed 1 day before termination of pregnancy. While the exclusion criteria were patients who did not do antenatal ultrasound and refused to participate in the study. In total there were 35 research subjects who were obtained through the consecutive sampling method. All subjects who met the criteria underwent an ultrasound examination and then scored with PAI and Tovbin. To prevent any bias, the ultrasound examination was done by one person. Confirmation of the diagnosis was known through uterine and placental histopathology. An analysis was carried out regarding the values of sensitivity, specificity, NDP, NDN, and accuracy in each scoring system and then statistical analysis was carried out using the Chi-Square test. This research has received ethical clearance from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University No. 1297/EC/KEPK-RSDK/2022.

RESULTS

Research subject in the study amounted to 35 people who met the inclusion and exclusion criteria. (Table 1) The characteristics of the study respondents were divided based on the patient's age, number of history of sectio caesarea, number of parity, gestational age, ante partum bleeding, length of stay, number of transfusions, preoperative Hb, postoperative Hb, baby's birth weight, APGAR score, amount of bleeding during surgery, postoperative ICU care, postpartum hemorrhage, hysterectomy, bladder injury, and intestinal injury.

TABLE 1
Subject Characteristics

Characteristics		Frequency (%)	Mean ± SD (Median)
Maternal Age	<20	0 (0)	
	20 – 35	24 (68.6)	
	>35	11 (31.4)	
Prior Sectio Caesarea	1x	15 (42.9)	
	2x	20 (57.1)	
Parity	2	13 (37.1)	
	>2	22 (62.9)	
Maternal Age	28 – 34	12 (34.3)	
	>34 – <37	20 (57.1)	
	>37	3 (8.6)	
Antenatal Bleeding	Yes	9 (25.7)	
	No	26 (74.3)	
Length of Stay	<5	5 (48.6)	
	5 – 7	15 (42.9)	
	> 7	3 (8.6)	
Hemoglobin level	Pre operative		10.65 ± 1.00 (8.9 – 13.0) 10.35 ± 1.47
	Post operative		(8.4 12.5)
Packed red cell transfusion	Not Transfusion	11 (31.4)	
	≥ 1	24 (68.6)	
Amount of bleeding	≤ 500 cc	13 (37.1)	1161.43 ± 1034.44 (967 – 1400)
	> 500 cc	22 (62.9)	
Post operative ICU	Yes	4 (11.4)	
	No	31 (88.6)	
Histerectomy	Yes	18 (51.4)	
	No	17 (48.6)	
Bladder Injury	Yes	7 (20.00)	
APGAR Score	*Vigorous baby*	33 (94.3)	
	Asphyxia	2 (6.7)	
Birth Weight (gram)	1500 – <2500	15 (42.9)	
	>2500	20 (57.1)	

All subjects received blood transfusions, both packed red cell (PRC), whole blood (WB), and fresh frozen plasma (FFP).

PAI and Tovbin scoring Scoring with PAI and Tovbin was carried out based on the results of the ultrasound examination of the subject. The mean Tovbin PAI score was 7.57 ± 2.02 (Table 3).

The scoring results were confirmed with the histopathological results of the PASD. The optimal cut off point value based on AUC (Area Under The Curve) in PAI scoring is 4.4. Scoring analysis using Tovbin with a cut off value of 7.5.

TABLE 2
PAI and Tovbin Score

Scoring Method	Mean ± SD
PAI	4.75 ± 1.22
Tovbin	8.09 ± 1.76

TABLE 3
***Cut off point* Scoring System**

Scoring methods		PASD (Histophatology)	
		PASD (+)	PASD (-)
PAI	≥4.4	23	1
	<4.4	6	5
Tovbin	≥7.5	25	1
	<7.5	4	5

TABLE 4
Diagnostic Test Analysis (PAI and Tovbin)

Parameter	Scoring Methods	
	PAI	Tovbin
Sensitivity (%)	79.31	86.21
Specificity (%)	83.33	83.33
Positive predictive value (%)	95.63	96.15
Negative predictive value (%)	45.45	55.56
Acc (%)	80	85.71
p	0.012*¥	0.002*¥
Relative risk (RR)	1.02 (3.03 – 4.51)	2.16 (1.04 – 4.51)

TABLE 5
PAI and Tovbin Scores Suitability Test

Scoring methods	Mean ± SD	Kappa
PAI	4.75 ± 1.22	
Tovbin	8.09 ± 1.22	0.742

Diagnostic Test Analysis (PAI and Tovbin)
Analysis of the diagnostic test with the PAI and Tovbin scoring systems showed that Tovbin had higher sensitivity, NDP, NDN and accuracy values compared to PAI while the specificity values for the two scores were the same ($p<0.05$).

Based on the results of the correlation and difference tests, it was statistically found that the use of PAI and Tovbin scoring had a significant relationship and difference ($p<0.05$). In addition to analysis related to diagnostic tests, analysis related to the suitability of the

results of use between scoring systems was also carried out (Table 5).

The results of the suitability test for the PAI and Tovbin scores indicated that the kappa index value was >0.6 so that it could be concluded that the suitability category between scoring systems was good.

DISCUSSION

The results of the study showed that the dominant PASD was at the age of 20–35 years. The correlation between age and PASD incidence was reported in a cohort study. The results of this study reported that the incidence of PASD increased at maternal age > 35 years.[16] These results were supported by epidemiological studies which reported an increased risk of PASD was found in women aged >35 years with other factors that could influence, including parity numbers, history of actions that could affect fertility, hormonal changes, and the site of implantation.[17] The differences found in the results of this study were associated with the average sample in the study being the productive age of mothers for pregnancy in Indonesia, namely ages 20–35 years.

All respondents in this study were multigravida. This is in accordance with previous studies which reported that 73.2% of patients with PASD were patients with multigravidas. Multigravida is associated with a history of previous pregnancies, especially a history of delivery by cesarean section and the condition of the uterus at the time.[18] Patients with a history of cesarean section have a 2.2x fold risk of experiencing PASD in subsequent pregnancies.[19] The increased risk rate increases in proportion to the frequency of previous cesarean sections. The risk of pregnancy with a history of cesarean section ≥2x can increase to 17x.[20] In conditions of pregnancy with surgical scars, both from a history of cesarean sections and other operative actions on the uterus, it causes implantation of the blastocyst into the hysterotomy scar and will cause a PASD condition.[21]

The elective caesarean section procedure is more at risk of experiencing PASD compared to the emergency caesarean section procedure. This is hypothesized through two mechanisms including differences in position technique, length, and healing time of incision wounds and better immune conditions after the onset of labor. The condition of the uterus in an emergency caesarean section tends to have adequate contractions so that the incision wound becomes shorter, damage to the endometrium becomes minimal and makes the tissue more potential for the healing period.[17]

The gestational age at the time of Caesarean section for the respondents in this study ranged from >34 – <37 weeks by 57.1% and >37 weeks by 8.6%. This is in line with a study in Vietnam 2022 where elective caesarean section was mostly performed at >37 weeks of gestation.

Assessment of Hb levels before and after surgery was carried out for all respondents. Most of the respondents (68.6%) needed PRC blood transfusions to overcome blood loss during the procedure. As many as 51.4% of respondents underwent hysterectomy and 11.4% were found to have complications from bladder injuries. The range of hospitalization for respondents was 2–13 days and 11.4% of them needed treatment in an intensive room.

The neonatal outcomes of this study were known to be 94.3% of babies born healthy with 42.9% of babies born with normal weight and 57.1% of babies born weighing ≥2500 grams. This is consistent with research on the neonatal outcomes of PASD patients where 78.5% of babies were born with a weight ≥2500 grams. Previous research in 2020 reported on patient outcomes after hysterectomy and conservative surgery for PASD indications. The determination of treatment is considered based on the results of the PAI score assessment and a definitive diagnosis is made intraoperatively. The use of the PAI score was significantly associated with diagnosing PASD ($p<0.001$).[22]

Based on the results of the PASD diagnostic test with the PAI scoring system in this study, the sensitivity value was 79.31%, specificity 83.33%, NDP 95.83%, NDN 45.45%, accuracy 80.00% with a cut-off value of 4.4. The PAI score scoring system includes a history of CS ≥2x, lacunae assessment using the Finberg William classification, myometrial thickness, placenta previa, and bridging vessels.[23] In the PAI scoring system, the degree of lacunae provides the maximum score weight that can change the final score. The greater the size and irregularity of the lacuna, the greater the risk of PASD. The use of Doppler images can improve the accuracy of the diagnosis because of its ability to identify a more accurate depth of placental invasion.[24]

Another predictor variable that influences the incidence of PASD is myometrial thickness. Myometrial thickness is an important predictor of PASD. A diagnostic study by Verma *et al* reported that the myometrial thickness variable had a sensitivity of 85.9%, a specificity of 71.4%, with a cut-off value of 0.88 mm in predicting the incidence of PASD.[25] The cut-off in this study was not much different from the PAI scoring system, where myometrial thickness ≤ 1 mm is given the highest score weight. The reduced myometrial thickness in PASD cases may be due to vascular abnormalities and placental invasion. Thus, variable myometrial thickness can be considered as a marker of abnormalities and functional abnormalities of the placenta.[26]

Diagnostic study of the PAI scoring system in predicting the incidence of PASD in 177 cases of placenta previa, 142 of whom were diagnosed with PASD. The sensitivity of using PAI reaches 75%, specificity 83% with a cut off value of 4.6.[23] The results of these studies with this study have a difference of approximately 1% in the

diagnostic component and 0.2 in the cut off. This shows that there is consistency in the use of the PAI scoring system.

Another scoring system was created to predict PASD morbidity, namely the Tovbin scoring. In our study, the results showed that the Tovbin score had an AUC value of 93.1% and the cut-off value of the Tovbin score based on placenta accreta was 7.5. From the results of the diagnostic test in this study, the sensitivity value was 86.21%, the specificity value was 83.33%, the positive predictive value was 96.15%, the negative predictive value was 55.56% and the accuracy value was 85.71%. The differences in the Tovbin and PAI scoring systems are in the description and assessment of the lacuna, the location of the placenta, the parameter of obliteration of the uretroplacental demarcation (loss of clear zone), and the use of Doppler in assessing the vascularization of the placenta urinary bladder (bridging vessel). Based on the components assessed, the Tovbin scoring system is considered more complete and simpler than PAI. The Tovbin scoring system assesses lacuna by describing the weight of the score based on size and number, while the PAI scoring system uses the Finberg William grading system.

Parameter of demarcation obliteration in the uteroplacental (loss of clear zone) is considered effective in predicting PASD. The utility for the parameter of the absence of demarcation at the uteroplacental boundary is based on the fact that trophoblastic tissue invasion of the myometrium and the absence of decidua basalis in invasive placentation can progressively lead to reduction of myometrial thickness and loss of space between the myometrium and placenta.

Another scoring parameter in Tovbin that is not included in the PAI is the assessment of lacunae blood flow using Doppler. Although in PAI scoring an assessment of bridging vessels is carried out, bridging vessels can only appear if there is a large amount of neovascularization.[27] The parameters in Tovbin assess in more detail regarding blood flow in the lacunae and hypervascularization of the placenta to the bladder.

The Tovbin scoring system began to be developed in 2016. The Tovbin scoring system is considered to have a high accuracy value in predicting PASD case. Research on the diagnostic test of the Tovbin scoring system was carried out involving 258 pregnant women with placental implantation abnormalities. The results of the study reported a sensitivity value of 69.6% and a specificity of 98.7%.[28]

Based on the results of a comparison using the Tovbin and PAI scoring systems in this study, it was found that the Tovbin scoring results had a sensitivity value that was almost as good as PAI while the specificity values were the same. From the results of this study, it was found that the tovbin score had a better accuracy value than the PAI score in predicting Placenta Accreta Spectrum Disorders (PASD). Based on the results of the kappa index value in the suitability test, it was concluded that the PAI and Tovbin scoring systems had good compatibility.

Results have proven that Tovbin significantly better scoring system for early detection of PASD. Its implementation should be done carefully by skillfull obstetric and gynecologic specialist during antenatal care in order to maximize the outcome and prevent bias existed due to ultrasound operator skill.

CONCLUSION

The Tovbin score has almost the same sensitivity and accuracy values and the same specificity value in predicting PASD compared to the PAI scoring system. It can be concluded that the two scoring systems have a good value fit. Tovbin score can be used by obstetricians and gynecology specialists in referral hospitals as an alternative diagnostic tool in predicting PASD events besides PAI scores, especially in patients with a history of 1x cesarean section with suspicion of PASD. We hope that future researh able to develop scoring system for early detection of PASD with better sensitivity and specificity score, hence adaptable for various diagnosis challenge condition of PASD.

Funding
This research did not receive a specific grant from a funding agency in the public, commercial, or not for profit sector.

Conflict of Interest
The authors certify that they have no competing financial interests or personal relationships that could influence the work reported in this paper.

Research Ethics
The research was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University Dr. Kariadi Semarang.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) :33–37

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Original Article

Comparison of The Effectiveness of High Intensity Laser Therapy (HILT) and Low-Level Laser Therapy (LLLT) on Improving Balance in Knee Osteoarthritis

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.984

Accepted: September 05th, 2023
Approved: December 19th, 2023

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Abstract

Background : Osteoarthritis (OA) of the knee is a joint disease with a high prevalence among the elderly. OA can cause balance disorders, which are one of the main causes of falls in the elderly. Balance can be measured using several scoring systems, one of which is the Berg Balance Scale (BBS). One of the treatment modalities for OA is laser therapy which is non-invasive and easy to apply. Low level laser therapy (LLLT) has been widely used in patients with knee OA, but recently high intensity laser therapy (HILT) has begun to be used in physical therapy with advantages over a wider range and depth. The aims of this study was to compare the effect of LLLT and HILT therapy on improving functional balance in the elderly with knee OA.
Methods : This research is a randomized controlled trial pre-test and post-test-controlled group design. The sampling method used in this study is the simple random sampling method. The sample size was 27 subjects and divided into two groups, the LLLT group (n=14) and the HILT group (n=13). Each subject received laser therapy sessions 2 times a week for 4 weeks. Balance was assessed using the BBS before and after the intervention.
Results : There was an increase in BBS scores before and after treatment in the HILT group ($p<0.001$) and in the LLLT group ($p<0.001$), with the increase in the HILT group (7.79 ± 2.16) significantly greater than in the LLLT group (3.08 ± 0.76) ($p<0.001$).
Conclusion : HILT improves balance score better than LLLT.

Keywords : Balance Knee, Laser Therapy, Osteoarthritis

INTRODUCTION

Osteoarthritis (OA) of the knee is a musculoskeletal joint disease that often occurs in the elderly. OA of the knee alone accounts for 50% of all rheumatological disorders.[1] Studies estimated that 70–85% of people aged over 60 years old experience OA with symptoms such as pain, joint stiffness, instability, and muscle weakness, which causes functional limitations and decreased quality of life. The prevalence of symptomatic knee OA is estimated at 3.8% globally, which is higher in women (4.8%) compared to men (2.8%).[2] Based on data from Riskesdas in 2018, the prevalence rate of knee OA in Indonesia is 15.5% for men and 12.7% for women.[3]

The leading cause of functional impairment and impairment in knee OA is pain, whereas osteophyte formation, cartilage damage, periarticular muscle spasms, and contractures cause a limited range of joint motion.[4] In addition, muscle weakness and impaired proprioceptive function in knee OA reduce neuromuscular protective mechanisms and increase joint instability, contributing to balance disorders. Impaired postural stability is one of the leading causes of falls in the elderly and is a significant public health problem.[5] The Berg Balance Scale (BBS) is the most widely known and widely used balance assessment among other balance measurement instruments. Using BBS as a balance measurement instrument is relatively easy, fast, and has a high degree of reliability.[6]

The management of knee OA includes pharmacological and non-pharmacological therapy. Laser is a non-invasive, painless, and easily administered modality to patients with OA. Low-Level Laser Therapy (LLLT) has been widely used as a non-pharmacological treatment in patients with knee OA for pain relief. LLLT exerts analgesia by altering nerve transmission or inhibiting sensory nerve activity to increase pain threshold. LLLT could also increase joint cartilage regeneration through the mechanism of chondrocyte synthesis proliferation and extracellular matrix secretion.[7]

Recently, High-Intensity Laser Therapy (HILT) was introduced to the field of physical therapy, which can reach and stimulate larger and deeper joints than LLLT. A distinguishing characteristic of HILT is the ability to produce photomechanical effects in tissues due to the very short duration and high intensity of the impulses. This phenomenon can have important therapeutic effects, as the stimulation can trigger biological signals to promote tissue repair and regeneration and activate the vascular and lymphatic systems.[8] Angelova *et al*. who studied the administration of 7 sessions of HILT therapy in patients with grade 2–3 knee OA showed significant improvement in the degree of pain and balance (static and dynamic) as measured using pedo barometric assessment.[1] Research on the effect of laser therapy on the balance of patients with knee OA is still limited, so this study aims to determine and compare the effect of HILT and LLLT administration on the balance of patients with knee OA.

METHODS

This research is a randomized controlled trial pre-test and post-test-controlled group design. The sampling method used in this study is the simple random sampling method. The research was conducted in Physical Medicine and Rehabilitation Clinic at RSUD KRMT Wongsonegoro, Semarang from August to September 2022. Patients aged 50–65 years old with bilateral grade 2–3 knee OA based on Kellgren-Lawrence classification, body mass index > 18 dan < 24 Kg/m^2, mild pain (VAS 0–3), not contraindicated for laser therapy, and were agreed to participate were included in this study. Patients with an acute inflammatory condition of the knee joint, neurological disorders affecting balance, cognitive impairment (MoCA-INA score <26), visual and vestibular disorders, lower extremity MMT strength <4, other musculoskeletal disorders, history of total knee replacement surgery or other knee surgery, deep lower extremity fractures in the last 6 months, intra-articular injections into the knee joint in the last 6 months, received viscosupplementation therapy in the last 7 days, or currently taking drugs that can affect balance were excluded from the study.

The participants were randomly allocated into 2 groups, HILT and LLLT. HILT was given using High Intensity Laser Device BTL-600 in 2 phases; phase 1 (analgesic effect) consist of continuous circular movements for 2 minutes, 10 watts power, application of pulses with a frequency of 25 Hz with 80% duty cycle, a dose of 12 J/cm^2, wavelength 1064 nm, and treatment area of 25 cm^2, continued with phase 2 (biostimulation effect), which consist of continuous linear motion for 4 minutes, 5 watts power, a dose of 120 J/cm^2, wavelength 1064 nm, treatment area of 25 cm^2. LLLT was given using Low Level Laser EME Polyeter Evo with a wavelength of 905 nm, 78mW power, a dose of 1.5 J/spot for 120 seconds in 6 spots. Each subject in both groups received 2 laser therapy sessions a week for 4 weeks. Balance was assessed using the BBS before and after the intervention.

The collected data were analyzed using SPSS software. The normality of the data was analyzed using the Shapiro Wilk test. For normally distributed data, the parametric statistics analysis was performed. Otherwise, the Kruskal Wallis test followed by the Mann Whitney test was used to determine differences between groups. A paired t-test was used to analyzed the difference before and after treatment in each group. The p value <0.05 with a 95% confidence interval were considered as statistically significant.

This research has received ethical clearance from

the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University Semarang with number 268/EC/KEPK/FK-UNDIP/VII/2022 and ethical clearance from the Research Ethics Committee of RSUD K.R.M.T. Wongsonegoro, Semarang City with number B/7065/070/IX/2022. All research subjects had asked for their consent by signing a written informed consent

RESULTS

Thirty-four patients were enrolled in this study, and there were 4 participants (3 with BMI >24 kg/m^2 and 1 with VAS pain > 3) who did not meet the inclusion criteria, so they were excluded from this study. Of the 30 participants who had the initial measurement, there were 1 participant from the LLLT group and 2 participants in the HILT group who did not come for therapy and could not be contacted by the researchers. Hence, a total of 14 participants in the HILT group and 13 participants in the LLLT group underwent the final measurement.

Demographic analysis showed that the mean age of the HILT group was older than the LLLT group (62.00 ± 3.47 vs 59.54 ± 3.67 years), with no significant difference found between the groups. No significant difference was found in the patient's gender, education level, BMI, length of time suffering from OA, MoCA-INA score, and level of physical activity between the groups (Table 1). So it can be concluded that the characteristics of age, gender, education level, BMI, length of time suffering

TABLE 1
Patients' Characteristic

Variables		Laser Therapy		p
		HILT	LLLT	
Age (year)		62.00 ± 3.47	59.54 ± 3.67	0.053‡
Gender	Male	4 (66.7%)	2 (33.3%)	0.362¥
	Female	10 (47.6%)	11 (52.4%)	
Education Level	Middle School	8 (61.5%)	5 (38.5%)	0.520‡
	High School	4 (36.4%)	7 (63.6%)	
	Bachelor	2 (66.7%)	1 (33.3%)	
Body Mass Index (BMI)		23.28 ± 1.39	23.47 ± 1.48	0.528‡
Duration of OA (year)		4.90 ± 3.06	4.96 ± 4.17	0.675‡
MoCA-INA Score		25.71 ± 1.33	26.77 ± 1.48	0.062§
Physical Activity	Low	9 (52.9%)	8 (47.1%)	1.000‡
	Moderate	4 (44.4%)	5 (55.6%)	
	Active	1 (100%)	0 (0%)	

Description: * Significant (p <0.05); ‡Mann Whitney; ¥Fisher's exact; §Independent t

TABLE 2
BSS Score Analysis

BBS	Laser Therapy		p
	HILT	LLLT	
Pre treatment	32.00 ± 10.42	29.15 ± 7.66	0.429§
Post treatmet	39.79 ± 11.31	32.23 ± 7.53	0.054§
p	<0.001¶*	<0.001¶*	
Difference	7.79 ± 2.16	3.08 ± 0.76	<0.001‡*

Description : *Significant (p <0.05); §Independent t; ‡Mann Whitney; ¶Paired t

from OA, MoCA-INA scores, and levels of physical activity were similar in the two groups and were not confounding variables in the study.

Paired analysis in both the HILT and LLLT groups showed no significant difference in the BBS values before treatment, and there was no significant difference in the BBS values after treatment between the HILT and LLLT groups. There was a significant difference in BBS scores before and after treatment in the HILT group, which showed improved functional balance in patients treated with HILT. Likewise with the LLLT group, where the BBS values before and after treatment showed significant differences, indicating improved patient balance. The Mann-Whitney test of the difference in BBS values before and after therapy showed a significant difference, where the difference in BSS values was found to be greater in the HILT group compared to the LLLT group (Table 2).

DISCUSSION

The characteristics of the research subjects, which included age, gender, education, BMI, duration of suffering from OA, and physical activity, showed that there were no significant differences in the characteristics of the study subjects in the two groups, indicating a similar population.

Laser therapy is one of the therapeutic modalities for patients with osteoarthritis, which is influenced by the amount of energy or power generated, the wavelength, and the time of therapy administration. LLLT has been widely used to treat musculoskeletal pain, with several studies showing that LLLT can suppress pain and inflammation, stimulate healing, and improve blood circulation. The healing and repair caused by laser therapy are one of its biostimulation properties, where laser therapy can increase the production of ATP and nucleic acids and increase the synthesis of collagen, which will trigger tissue regeneration. The development of HILT offers a modality capable of delivering high-energy lasers in a shorter time and significantly deeper tissue penetration.[9]

This study used BSS to quantify the balance function of patients with OA, and Kim *et al*. have shown that BBS values in patients with moderate-to-severe OA are significantly lower than those with mild OA.[10] Balance involves the interaction between sensory input from the proprioceptive, visual, and vestibular systems, motor systems, and cognitive components, to maintain the body's center of mass on a pedestal. OA can affect a person's balance, and it has been reported that patients with OA have reduced proprioceptive sensation and muscle strength around the joints.[11] Our study found that the BBS score before and after therapy according to the intervention group of each subject had a significant difference, indicating that both modalities of laser therapy can improve knee balance function. The difference in BBS scores between before and after therapy was significantly greater in subjects who received HILT therapy, indicating that HILT was more effective in improving patients' balance function.

Patients with OA are often associated with joint edema resulting in proprioceptive disturbances, and some studies suggest that this condition results from loss or distortion of afferent feedback from the mechanoreceptors innervating the affected joints.[12] Research by Cho *et al*. found that fluid within the joint contributes to proprioceptive deficits in knee OA. The presence of distention of the hypertrophied joint capsule in OA conditions is the cause of proprioceptive disturbances.[13] Laser therapy is known to have the ability to cause biostimulation in damaged tissue. The laser can trigger the repair of the mechanoreceptors in the joint, where it is known that type I mechanoreceptors (Ruffini receptors) and type 2 (Pacini receptors) are the main types of mechanoreceptors located in the joint capsule.[14]

OA is known to involve a chronic and low-grade inflammatory process in its pathogenesis.[15] Laser therapy was found to modulate inflammatory activity and accelerate wound healing, by a study by Stergioulas *et al*. reported the ability of LLLT to reduce swelling in sprained ankle joints. It was explained that laser therapy could promote vasodilation, increase blood flow and lymph drainage, and activate fibroblasts and neutrophils, which will cause changes in pain threshold and reduce edema.[16]

Laser therapy is also widely used to improve muscle strength and repair. The study by Alghadir *et al*. found that administering LLLT to patients with knee OA improved functional performance, reflecting improvements in muscle strength. The more significant improvement of knee balance in OA patients with HILT administration could be due to its ability to produce a photomechanical effect on the treated tissue due to its short duration and high light intensity.[17] Stimulation of HILT can trigger biological signals that promote tissue repair and regeneration, along with activation of the vascular and lymphatic systems, which improve muscle function.[8]

This research has several limitations. First, this study only measured the final result of the total BBS score and did not analyze the differences in each component of the BBS score assessment. Second, this study only analyzed the balance function in terms of sensory components; because the research subjects did not receive an exercise program, there was no assessment and analysis of the motor components of balance, such as muscle strength.

CONCLUSION

High-intensity laser therapy (HILT) and low-level laser therapy (LLLT) resulted in improvements to the Berg

Balance Scale balance score in patients with knee OA, with an increase in the post-treatment Berg Balance Scale balance score in the HILT group, which was higher than in the LLLT group.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 38–44

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Original Article

Relationship between Serum Malondialdehyde (MDA) Levels with Seizure Frequency in Epilepsy Patients with Combination of Phenytoin and Valproic Acid

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.987

Accepted: August 14th, 2023
Approved: December 19th, 2023

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Abstract

Background : Oxidative stress is believed to be one of the factors involved in the pathogenesis of epileptogenic where lipid peroxidation occurs which produces Malondialdehyde (MDA). Epilepsy and some Antiepileptic Drugs (AEDs) can improve or worsen seizure frequency thereby significantly changing blood MDA levels. The objectives of this study was to determine the relationship between serum MDA levels and seizure frequency in epileptic patients treated with AEDs, a combination of phenytoin and valproic acid.

Methods : A cross-sectional study with consecutive sampling of 46 subjects (with epilepsy receiving combination therapy with phenytoin and valproic acid. The research was conducted at the Neurology Policlinic at RSUP Dr. Kariadi in December 2022 – February 2023. MDA levels were measured using the Enzyme Linked Immunosorbent Assay (ELISA) method. The relationship between serum MDA levels and seizure frequency was analyzed using Spearman's test since both of the variables are ordinal scale, the results were significant if $p<0.05$.

Results : There was no relationship between MDA levels and seizure frequency in epileptic patients with the combination of phenytoin and valproic acid. ($p=0.516$) There is a significant relationship between the frequency of seizures and the length of treatment ($p=0.026$) with a weak negative correlation ($rho=0.328$). There is a significant relationship between the frequency of seizures and the age of onset of epilepsy ($p=0.037$) with a weak negative correlation ($rho=0.309$).

Conclusion : There is a significant relationship between the frequency of seizures with the length of treatment and the age of onset of epilepsy.

Keywords : MDA, frequency of seizures, length of treatment, age of onset of epilepsy

INTRODUCTION

Oxidative stress is believed to be one of the factors involved in the pathogenesis of epileptogenesis.[1,2] The brain and nervous system are very vulnerable to lipid peroxidation because lipid membranes are very rich in polyunsaturated fatty acid chains that can increase peroxidation and prevent neuron regeneration[3–5] and can exacerbate some forms of seizures.[6–8]

A review of studies conducted on epilepsy and oxidative stress showed that the parameters of oxidative stress increased.[9] Lipid peroxidation is an indicator of free radical metabolism and oxidative stress in humans and other organisms. Among the aldehydes produced from lipid peroxidation, Malondialdehyde (MDA) and 4-hydroxynonenal (HNE) have received the most attention, because MDA is produced in large quantities during lipid peroxidation, so it is generally used to measure the level of oxidative stress, being a simple and easy marker to determine Lipid peroxidation due to oxidative stress in human subjects.[10,11] The serum MDA level in healthy individuals is 0.8 ± 0.20 µmol/L.[12]

Epilepsy causes increased oxidative stress and increases MDA levels.[13] MDA levels are affected during administration of anti-epileptic drugs (OAE).[14] Many studies have shown a significant increase in peripheral blood MDA serum levels in epileptic patients compared to controls, but none has assessed the relationship between MDA serum levels and seizure frequency in epileptic patients.

Dr. Kariadi hospital is a referral hospital where epilepsy patients referred from regional hospitals who have previously taken anti-epileptic drugs are referred because their seizures have not been resolved. This is what underlies the fact that the majority of epilepsy patients at Dr. Kariadi hospital in the BPJS era received combination drug therapy, including phenytoin and valproic acid.

METHODS

This research is an observational study with a cross sectional approach. The inclusion criteria included all epilepsy patients with the main combination therapy of phenytoin and valproic acid with a length of treatment of more than 6 months because shorter treatment duration was significantly associated with higher seizure frequency, subjects who received anti-epileptic treatment for one to five years and those for more than five years had a lower prevalence of risk of increased frequency of seizures. The next inclusion criteria are aged 18–60 years and patients who were cooperative and willing to participate in the research program by signing an informed consent. Exclusion criteria included secondary epilepsy with a history of mass etiology in the brain, trauma, infection and patients with hypertension, DM and chronic kidney disease. The selection of research subjects was by consecutive sampling, sample selection by determining subjects who meet the inclusion criteria and are included in the research for a certain period of time. Based on the Lameshow formula, there were 46 research subjects. In this study, the independent variable was the serum MDA level, namely the median cubital vein blood MDA level in blood plasma which was examined using the ELISA spectrophotometric method and expressed in units of µmol/l. The normal serum MDA level is 0.8 ± 0.20 µmol/L which is an ordinal scale grouped into: normal MDA levels (600 – 1000 pg/mL), increased MDA levels (more than 1000 pg/mL), decreased MDA levels (less than 600 pg/mL). The dependent variable is the frequency of seizures, namely the number of seizures that occurred in the last 1 year, obtained from anamnesis and medical records, divided into less than 10 times and more than or equal to 10 times, which is an ordinal scale. Duration of treatment and age of onset were confounding variables, both being ordinal scales. The duration of treatment was obtained from the history and medical records, namely the duration of treatment for a combination of phenytoin and valproic acid, which was divided into more than or equal to 5 years and less than 5 years. Age of onset is the age at which the patient was diagnosed with epilepsy obtained from the history and medical records, divided into age more than 24 years and age 18–24 years.

This research was conducted in December 2022 – February 2023 at the Outpatient Installation of the Merpati Neurology Polyclinic, RSUP Dr. Kariadi Semarang. The research was carried out by requesting approval from the Medical Research Ethics Committee of FK UNDIP/RSUP Dr. Kariadi with number 1247/EC/KEPK-RSDK/2022. The research subjects underwent neurological examination and blood laboratory examination of serum MDA levels. Blood samples were examined in the GAKI laboratory. The MDA examination procedure, namely the venous blood sample is stored in a tube then centrifuged and serum is collected. Examination of MDA serum levels was carried out using the ELISA method, with an ELISA kit produced by Elabscience (Catalog No: E-EL-0060), then the results were recorded and the data analyzed.

The data that has been collected is checked for completeness and correctness, then the coding process is carried out, tabulated and processed to a computer using a statistical software program. Results are presented in tabular form. To determine the relationship between serum MDA levels and seizure frequency in epileptic patients with a combination of phenytoin and valproic acid, Spearman's correlation test was performed with a 95% confidence level. Confounding variables, namely duration of treatment and onset of epilepsy, were subjected to a bivariate test using the Spearman correlation test. Results are said to be significant if $p < 0.05$.

RESULTS

There were 46 subjects obtained in this study who met the inclusion criteria.

This study used 46 subjects, consisting of 29 male subjects (63%) and 17 female subjects (37%). Based on age, there were 40 subjects aged 19–44 years (87%) and 6 subjects aged more than or equal to 45 years (13%). A total of 8 subjects had elementary school education (17.4%), 5 junior high school subjects (10.9%), 21 high school subjects or equivalent (45.7%), 2 D3 subjects (4.3%) and 10 S1 subjects (21.7%). Based on the type of work, 6 subjects did not work (13%), 8 student subjects (17.4%), 9 housewife subjects (19.6%), 12 self-employed subjects (26.1%), 9 private employee subjects (19.6%) and 2 subjects Civil servants (2%). Based on therapy, 25 subjects received combination therapy with phenytoin and valproate (54.3%) and 21 subjects received combination therapy with phenytoin, valproic acid and other OAE (45.7%) (Table 1).

A total of 46 samples were taken to check serum MDA levels and the results obtained were 7 subjects with MDA levels of 600–1000 pg/mL (15.2%), 12 subjects with MDA levels >1000 pg/mL (26.1%) and 27 subjects with levels MDA <600 pg/mL (58.7%). Based on the anamnesis, it was found that 17 subjects had a frequency of seizures in 1 year of less than 10 times (37%) and 29 subjects with a frequency of seizures in 1 year of more than or equal to 10 times (63%). A total of 25 subjects received the main combination therapy with phenytoin and valproic acid for more than 5 years (56.5%) and 21 subjects received the main combination therapy with phenytoin and valproic acid for less than 5 years (43.5%). In anamnesis, there were 28 subjects with age of onset of epilepsy more than 24 years (60.9%) and 18 subjects with age of onset of 18–24 years (39.1%) (Table 2).

Based on Table 3, the Sperman correlation test found no relationship between serum MDA levels and seizure frequency in epileptic patients on combination therapy with phenytoin and valproic acid (p=0.516) with a very weak negative correlation rate (rho=-0.098). (Hypothesis 1 is not proven). There was a significant relationship between the frequency of seizures and the length of treatment in patients on combination therapy with phenytoin and valproic acid (p=0.026) with a weak negative correlation rate (rho=-0.328), the longer the

TABLE 1
Characteristics of research subjects

Variable		Epilepsy patient Total (n=46)	
		f	%
Gender	Man	29	63
	Woman	17	37
Age	19-44 years	40	87
	≥ 45 years	6	13
Education	SD	8	17.4
	SMP	5	10.9
	SMA/SMK/MA	21	45.7
	D3	2	4.3
	S1	10	21.7
Work	Doesn't work	6	13
	Student	8	17.4
	Housewife	9	19.6
	Self-employed	12	26.1
	Private sector employee	9	19.6
	Civil servant	2	4.3
Therapy	Phenytoin and valproic acid	25	54.3
	Phenytoin, valproic acid and other OAEs	21	45.7

TABLE 2
Results of research variable data

Variable		Epilepsy patient Total (n=46)	
		f	%
MDA levels (pg/mL)	600–1000	7	15.2
	>1000	12	26.1
	<600	27	58.7
Awakening frequency	Less than 10 times	17	37
	≥ 10 times	29	63
Treatment duration	≥ 5 years	26	56.5
	< 5 years	20	43.5
Age of onset of epilepsy	Over 24 years	28	60.9
	18 – 24 years	18	39.1

TABLE 3
Relationship between seizure frequency and MDA serum levels, length of treatment and age of onset of epilepsy

Variable	rho	p.s	Significance
MDA Serum Levels	-0.098	0.516*	Meaningless
Treatment duration	-0.328	0.026*	Meaningful
Age of Onset of Epilepsy	-0.309	0.037*	Meaningful

*Spearman Correlation Test is significant if $p<0.05$

treatment, the frequency of seizures will decrease. (Hypothesis 2 is proven). There is a significant relationship between the frequency of seizures and the age of onset of epilepsy in patients on combination therapy with phenytoin and valproic acid (p=0.037) with a weak negative correlation rate (rho=-0.309).

DISCUSSION

Relationship between Serum MDA levels and seizure frequency

In this study, there was no association between serum MDA levels and seizure frequency in epileptic patients on the main combination therapy with phenytoin and valproic acid (p=0.516) with a very weak negative correlation rate (rho=-0.098). There are several factors that affect MDA levels including the anti-epileptic drugs used. The drugs that increase GABA-ergic transmission (eg, vigabatrin, tiagabine, gabapentin, topiramate) or other antiepileptics (eg, lamotrigine, levetiracetam) reduce neuronal oxidation markers.[15] Valproic acid shows a significant antioxidant effect by reducing MDA levels. This can lead to a decrease in seizure activity that occurs due to the efficacy of OAE and the simultaneous neuroprotective effect of ROS modulation.[16] Erythrocyte MDA levels increased significantly among people with epilepsy compared to the control group, indicating the formation of free radicals in epilepsy. The results of this study on post-treatment epilepsy subjects showed that antiepileptic drugs can provide antioxidant effects and the addition of antioxidants to conventional drug therapy can increase further reductions in epileptic activity; also helps restore the antioxidant balance to normal status among epileptic subjects.[17] MDA levels were higher in the control group and this difference was statistically significant. It is thought that the lower MDA levels in epileptic patients may be due to the antiepileptic drugs used. In this case, MDA levels should be lower in patients undergoing polytherapy, while MDA levels should be higher in patients undergoing monotherapy compared to those undergoing polytherapy. This suggests that the type of antiepileptic drug used is also important at the MDA level. In a different experimental study, it was reported that MDA levels decreased with ethosuximide,

phenytoin and primidone.[13]

Other factors that affect serum MDA levels include a study in 97 DM patients with a control of 50 healthy people showing a significant increase in MDA levels in DM patients compared to controls.[12] Meanwhile, study of 82 DM patients found that consumption of vegetables, fruits, legumes and nuts was associated with lower MDA levels.[12] It was found that the average MDA level was highest in the hypertensive group, followed by prehypertension and the group of healthy subjects.[18] Study on 50 hypercholesterolemic subjects and 50 healthy control subjects showed that subjects with hypercholesterolemia had significantly higher MDA levels compared to healthy control subjects.[19] A study of 21 obese subjects with a control of 21 non-obese subjects, the results of which showed that the MDA levels of obese subjects were significantly higher than those of non-obese.[20] Another supporting study was conducted on 300 DM subjects with a control of 100 healthy subjects, showing that there was a significant positive relationship between the increase in BMI and MDA serum levels.[21] In several studies, higher serum MDA levels were found in CKD patients compared to healthy control subjects.[22] MDA levels increase with the development of kidney damage.[23] MDA was negatively correlated with glomerular filtration rate and differed significantly among patients with CKD stages 2, 3, 4, and 5. Higher serum MDA levels were also found in hemodialysis patients.[24] Serum MDA levels in kidney transplant patients were significantly lower than in dialysis patients.[25]

Based on the research there are factors that influence the emergence of the frequency of arousals including respondents who reported lack of sleep in the last 2 months had a 41% rate (AIRR = 1.41, 95% CI [1.02, 1.94]) the rate of occurrence of seizures higher than their counterparts. Studies from Denmark and Norway also support this finding. Seizure frequency in patients with generalized epilepsy was found to be very sensitive in sleep-deprived patients.[26] This study also found that responders who adhered to their OAE treatment had a lower risk of seizures which increased the probability of a score of zero for seizure frequency compared to non-adherents. This is in line with a retrospective study and a cross-sectional study that found a statistically significant association between a higher risk of seizures and non-adherence to OAE. A pilot survey of the association between poor medication adherence and seizures also found a statistically significant association between drug dosage lost and a higher risk of revival attacks.[27] In the study it was found that emotional stress was the most frequently reported trigger in this study. Based on clinical experience and the results of these studies have shown a strong relationship between the occurrence of emotional stress and/or tension and the occurrence of seizures. Temkin and Davis claim that difficulties in everyday life increase the risk of increased seizures, while pleasurable experiences have the opposite effect.[28] The opinion that emotional stress lowers the arousal threshold is also consistent with the results of psychopharmacological and behavioral intervention studies, in which reduced levels of stress and anxiety are associated with decreased arousal frequency.[29] Among those who reported seizure triggers, 4.4% indicated they were sensitive to flickering light. This figure is consistent with previous findings that 5% of people with epilepsy are photosensitive.[28] Alcohol consumption was the fourth most frequent trigger (5.7%) of study participants. Given a person's reluctance to admit alcohol use, these results may represent an underestimation. Similar concerns related to reports of OAE drinking non-adherence (3.7%). It is therefore very possible that the reported frequency of alcohol use and medication nonadherence as seizure triggers may not reflect the actual results. Some women (3.3%) reported that their seizures were triggered by menstruation, as many women reported an increased frequency of menstrual cramps from a seizure diary, which often indicated that seizures did occur throughout the menstrual cycle.[28]

The relationship between the frequency of seizures and the duration of treatment

There was a significant relationship between the frequency of seizures and the length of treatment in patients receiving combination therapy with phenytoin and valproic acid (p=0.026) with a weak negative correlation (rho=-0.328). This is in accordance with the study of Kaddumukasa *et al* (2013), where subjects who had received antiepileptic drugs for more than one year had reduced seizure frequency with a p value of 0.0001. Shorter treatment duration was significantly associated with higher seizure frequency. Subjects who received anti-epileptic medication for one to five years and who for more than five years had a lower prevalence of increased risk of seizures.[30] Based on the research, it was also found that the frequency of seizures increased when the duration of treatment was less than five years.[26] However, in a study found a statistically significant positive relationship between treatment modalities and seizure attacks. Respondents who had undergone two or more treatments at the same time had a higher incidence of seizure attacks than those who had only used one treatment. The possible reason is that polytherapy increases the potential for drug-drug interactions, can affect adherence and is associated with higher costs of treatment. treatment for therapeutic drug monitoring.[31]

Relationship between seizure frequency and age of onset of epilepsy

There was a significant relationship between the frequency of seizures and the age of onset of epilepsy in patients on combination therapy with phenytoin and

valproic acid (p=0.037) with a weak negative correlation rate (rho=-0.309). This is in accordance with the study which found that the highest age of onset of epilepsy was 15–24 years (42.89%). In the study it was found that the highest frequency of epilepsy was found at the age of onset 15–24 years (56.35%). This study found an association between age and seizure frequency, indicating that patients in the 25–34 age group had a lower incidence of seizures than those in the 15–24 age group. This is different from a study conducted in the United States, which showed no significant correlation between change in seizure frequency from baseline to late follow-up and age. This could be because patients aged 25–34 years may have good adherence compared to those aged 15–24 years.[31] In the study 47% of patients had an age of onset <40 years, 38% of patients were between 41–60 years, and 15% were over 60 years.[32] Similar findings were reported where 46.9% were in the 21–40 year age group similar to other studies from India and other developing countries. In contrast, in studies in developed countries the number of patients with the age of first seizure onset was more in the age group >60 years with EPIMART (48.1%); Lars Forsgren (41.8%); Perre Jallon (40.1%). This variation may be because, in developing countries and rural areas, first seizures occurring in the elderly are often overlooked. India's main population belongs to the age group of 21–40 years, so the number of first seizure patients in this group is higher when compared to the elderly (>60 years).[33]

RESEARCH LIMITATIONS

This study has limitations including not assessing the factors that influence MDA levels including blood sugar levels, cholesterol levels, urea-creatinine levels, food recall and BMI status. This study did not assess the precipitating factors that influence the high frequency of seizures including the level of emotional stress, the level of adequate sleep, the level of fatigue, the level of alcohol consumption, the amount of light exposure and the level of adherence to taking OAE. This study did not record the frequency of awakenings using an awakening diary. In addition, this study did not assess the dose of phenytoin and valproic acid used in relation to the frequency of seizures.

CONCLUSION

There was no relationship between serum MDA levels and seizure frequency in epileptic patients with the combination of phenytoin and valproic acid. There is a relationship between the frequency of seizures and the duration of treatment in epilepsy patients with a combination of phenytoin and valproic acid. There is a relationship between the frequency of seizures and the age of onset in epilepsy patients with the combination of phenytoin and valproic acid.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 45–52

OPEN ACCESS

Original Article

Characteristics and Risk Factor of Multidrug-Resistant-Organism Infection in the Pediatric Intensive Care Unit of Dr. Kariadi Hospital Semarang

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.989

Accepted: July 05th, 2023
Approved: November 03th, 2023

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Publisher's Note:
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Abstract

Background : The Pediatric Intensive Care Unit (PICU) that treats critical patients with various invasive procedures is a potential place for Multidrug Resistant Organism (MDRO) infections. This spesific unit, especially in tertiary care facilities may have higher prevalence of MDRO than non-PICU settings, causes serious disease and mortality. The aims of this study was to describe the characteristics and risk factor of MDRO infection in the PICU of dr. Kariadi Hospital Semarang,
Methods : Retrospective study in patients aged 1 month – 18 years with growth of germs on culture results during 2021–2022. Demographic data, use of central venous catheters and ventilator, length of stay, duration of antibiotic usage, and history of major surgery were investigated from medical records. The amount of risk expressed by the Odds Ratio (OR).
Results : From 544 culture examinations, 199 (36.5%) germs grew, consisting of 79 MDRO isolates (39.7%) and 120 non-MDRO isolates (60.3%). Gram-negative bacteria were found in 140 samples (70.4%) with *Klebsiella pneumoniae* as the most common germ (15.1%) and respiratory tract infection (56.3%) being the most common infection diagnosis. As many as 24 of 30 (80%) isolates that grew *Klebsiella pneumoniae* were MDRO. Mechanical ventilator use (OR 2.15; 95% CI 1.07 – 4.3; p=0.043) and length of stay in the PICU (OR 2.44; 95% CI 1.21 – 4.96; p=0.018) are risk factors for MDRO infection.
Conclusion : *Klebsiella pneumoniae* is the most common germ found from culture isolates and respiratory tract infection is the most common diagnosis. The use of mechanical ventilators and length of stay in the PICU are risk factors for MDRO infection.

Keywords : risk factor, culture, MDRO, PICU, antibiotic resistance

INTRODUCTION

Multidrug Resistant Organism (MDRO) is defined as insensitivity or resistance of a microorganism to several antibiotic drugs.[1,2] Drug resistance can be occur due to natural phenomenon, selective pressure, and widespread distribution of pathogenic microorganisms.[3] These are several microorganism categorized as MDRO: Extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBLs), methicilin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Acinetobacter baumannii, Vancomycin-resistant Enterococci (VRE), dan Carbapenem-resistant enterobacteriaceae (CRE).[4]

Rising number of MDRO cases creating a emergent global problem nowadays.[5] World Health organization (WHO) predicted that MDRO cases causing 700.000 deaths in general population, while around 200.000 deaths in new born babies every year. It is estimated that 23.000 and 25.000 deaths per year in United States of America (USA) and Europe.[6] In Indonesia, prevalence of MDRO cases are rising every year. Based on National Survey on Antimicrobial Resistance by Ministry of Health in 2016, the prevalence of MDRO case especially for *E. coli* and *K. pnemunoiae* resulting ESBL are 50–82%. *Indonesia Antimicrobial Surveillance System* (INASS) in 2019–2020 showed that prevalence of cephalosporin-resistant and fluoroquinolone-resistant *E. coli* are 66.7% and 65.6%, respectively. While the number are higher for *K. pneumoniae*, 74.4% and 53.2%, respectively.[7,8]

Pediatric Intensive Care Unit (PICU) is a dedicated unit aimed to provide best care for critically ill patients with various invasive procedures and highly-potential place for MDRO cases to be found.[9] Immature immune system in children, prolong intensive care, such as intubation and central-venous catheter, and inappropriate wide-spectrum antibiotics are several causes that create PICU patients are highly vulnerable of being a MDRO case. MDRO cases are emerging problem in healthcare facilities, that causing more mortality, morbidity, prolonged length-of-stay, and increasing healthcare costs.[5] A study in Jordan showed that sepsis caused by MDRO had higher mortality than non-MDRO (60% vs 13%). Studies in Taiwan also showed that the Gram negative MDRO group had higher morbidity in neurological sequelae, kidney disease, use of parenteral nutrition, than the Non MDRO group. This study also found a longer duration of hospitalization in sepsis patients with MDRO compared to non-MDRO sepsis patients (27.6 days vs 20.7 days).[10]

MDRO infection case in PICU setting are vary. Infection pattern, hospitalized-cases complexity, bacterial pattern, and local antibiotic sensitivity creating vast major problem in MDRO infection. Several conditions are predicted to be the risk factor of MDRO indection in PICU setting, such as nutritional status, age, invasive device usage (intubation and mechanical ventilator, central venous catheter, and urine catheter), previous history of major surgical procedure, antibiotic use, and hospitalization period.[11–13]

This study aims to identify the characteristics and risk factor of MDRO infection in PICU setting of Dr. Kariadi General Hospital, which is a tertiary referral hospital in Central Java, where this kind of research has not been carried out much in this hospital. This research hopefully can be used as fundamental consideration for future prevention, management, and research of MDRO infection cases.

METHODS

This research was an analytical observational type with a retrospective approach, carried out in the PICU of RSUP Dr. Kariadi Semarang in all pediatric patients aged 1 month – 18 year during study period (January 2021 – December 2022). Patient with infection diagnosis (respiratory tract infections, abdominal infections, CNS infections, post-operative infections, urinary tract infections, skin infections) were taken based on antibiotic culture and lab results. Research subject characteristics data (gender, diagnosis of infection, type of germ, clinical outcome, and type of specimen) were extracted from medical records. The types of culture specimens taken include sputum, blood and urine specimens. Incomplete medical record data were excluded. Sample selection was carried out by total sampling. Data analysis were done using descriptive analysis and hypothesis testing. Analysis were done by dividing microorganism into two groups, MDRO and non-MDRO group. MDRO group is group of microorganism that has been proven to be resistant to at least one from ≥3 antibiotics.[4] The independent variables in this study were age, nutritional status, use of invasive medical equipment (CVC), use of a mechanical ventilator, length of treatment, duration of antibiotic use, and history of major surgery. Bivariate analysis were done by using Chi Square test. Odd Ratio and 95% Confidence Interval (CI) were defined as the risk of incidence of MDRO infection. This study has been approved by Ethical Committee of Faculty of Medicine, Diponegoro University, Semarang No. 1379/EC/KEPK-RSDK/2022 on January 13rd, 2023.

RESULTS

During the study period, the researcher has been able to register 544 culture examination from various specimens, 199 (36.5%) culture results were successfully grown microorganisms, consisting of 79 isolated MDRO microorganisms and 120 isolated non-MDRO microorganisms. Subjects' characteristics are shown in Table 1. There are 100 (50.3%) men and 99 (49.7%) women in this study. The most commonly found infection diagnosis are 112 cases (56.3%) of respiratory-tract

TABLE 1
Subjects Characteristics

Description		n (%)
Sex	Men	100 (50.3%)
	Women	99 (49.7%)
Clinical Diagnosis	Respiratory tract infection	112 (56.3%)
	Abdominal infection	21 (10.6%)
	Central nervous system infection	20 (10.1%)
	Urinary tract infection	22 (11.1%)
	Post-operative infection	21 (10.6%)
	Skin infection	3 (1.5%)
Causative Bacteria		
Gram-negative	*Klebsiella pneumoniae*	30 (15.1%)
	Pseudomonas Aeruginosa	27 (13.6%)
	Acinetobacter baumani	22 (11.1%)
	Eschericia coli	19 (9.5%)
	Stenotrophomonas maltophilia	18 (9.0%)
	Enterobacter spesies	10 (5.0%)
	Other species	8 (4.0%)
	Serratia marcescens	6 (3.0%)
Gram-positive	Other species	25 (12.6%)
	Staphylococcus epidermidis	17 (8.5%)
	Enterococus spesies	10 (5.0%)
	Staphylococcus aureus	7 (3.5%)
Outcomes	Survive	103 (51.8%)
	Death	96 (48.2%)
Culture specimen	Urine	20 (10.1%)
	Blood	69 (34.7%)
	Sputum	110 (55.3%)

infection, 22 cases (11.1%) of urinary tract infection, 21 cases (10.6%) of postoperative infection and abdominal infection, and 20 cases (10.1%) of central nervous system infection. Gram-negative bacteria were found in 140 sample (70.4%) and gram-positive bacteria were found in 59 sample (29.6%). From all examined culture specimens, *K. pneumoniae* (80%) is the most commonly found in MDRO infection cases.

After assigning each data based on the specimen type, it has been found that sputum is the most frequently examined specimen, followed by blood and urine culture. From 110 examined isolated sputum cultures, 85 of them were taken from patients using mechanical ventilators (773%), and 25 of the specimens were taken from patients without mechanical ventilators (22.7%). Bacterial groups are dominated with gram-negative bacteria with 91 isolate (84%), which 49 of them (44.5%) were assigned to MDRO group and 61 of them (55.5%) were assigned to non-MDRO group. The most commonly found bacterial in sputum culture are *K. pneumoniae* (20.9%). Gram-positive bacteria were found in 18 isolate (16%), which *Coagulase Negative Staphylococcus* has the largest numbers (6.4%).

Analysis results from 69 blood culture isolates, 21 of them are MDRO group isolates (30.4%) and 48 of them are non-MDRO group isolates (69.6%). Thirty five

TABLE 2
MDRO Prevalence in Various Infectious Pathogens

Microorganism		Non MDRO	Non MDRO
Gram-negative	*Klebsiella pneumoniae*	24 (80%)	6 (20%)
	Acinetobacter baumanii	16 (72.7%)	6 (27.3%)
	Pseudomonas Aeruginosa	5 (18.5%)	22 (81.5%)
	Enterobacter spesies	6 (60%)	4 (40%)
	Escherichia coli	16 (88.9%)	3 (11.1%)
	Stenotrophomonas maltophilia	0 (0%)	18 (100%)
	Serratia marcescens	3 (50%)	3 (50%)
Others	*Salmonella spesies*	2 (100%)	0 (0%)
	Chryseobacterium gleum	2 (66.7%)	1 (33.3%)
	Klebsiella aerogenes	0 (0%)	1 (100%)
	Aeromonas veronii bv veronii	0 (0%)	1 (100%)
	Burkholderia cepacia	0 (0%)	1 (100%)
Gram-positive	*Staphylococcus aureus*	0 (0%)	7 (100%)
	Staphylococcus epidermidis	2 (11.8%)	15 (88.2%)
	Enterococus spesies	3 (30%)	7 (70%)
Others	*Staphylococcus haemolyticus*	0 (0%)	7 (100%)
	Staphylococcus hominis	0 (0%)	8 (100%)
	Micrococcus luteus	0 (0%)	1 (100%)
	Streptococcus pneumoniae	0 (0%)	1 (100%)
	Staphylococcus capitis	0 (0%)	5 (100%)
	Staphylococcus cohnii	0 (0%)	1 (100%)
	Streptococcus mitis	0 (0%)	1 (100%)
	Streptococcus pyogenes	0 (0%)	1 (100%)

isolates were gram-positive (51%) and 34 were gram-negative (49%). The most commonly found gram-positive bacteria were *Coagulase Negative Staphylococcus* (24.6%) and *Staphylococcus epidermidis* (14.5%), while the most commonly found gram-negative bacteria were *A. baumanii* (11.6%), *P. aeruginosa* (10.1%), and *E. coli* (8.7%).

Urine specimens examination revealed that 9 out of 20 isolate were assigned to MDRO groups (45%). Fourteen isolates were gram-negative bacteria (70%) with the most commonly found bacteria are *E. coli* (30%) and *K. pneumoniae* (20%), while for gram-positive bacteria, *Enterococcus sp.* is the most common found in urine specimens.

Table 3 showed the results of bivariate analysis of study data. Data analysis revealed that nutritional status, CVC, previous history of major surgery, prolonged usage of antibiotics (≥7 days), and age were not significantly different in both study groups (p>0.05). While mechanical ventilator usage (OR 2.15; 95% CI 1.07 – 4.3; p = 0.043) and ≥ 9 days of length-of-stay (OR 2.44; 95% CI 1.21 – 4.96; p = 0.018) were significantly different in both study groups.

DISCUSSION

The percentage of MDRO varies in each country depending on the population and time of study. In 2021, a nation-wide study from Egypt reported that 9.2% prevalence of MDRO infection in PICU setting, while the previous study also mentioned that MDRO rates was 85.5% in septic patients treated in PICU and NICU

TABLE 3
Risk Factor of MDRO

Variables		MDRO		p	OR	95%CI
		Yes (n=79)	No (n=120)			
Nutritional Status	Malnutrition	33 (41.8%)	68 (53.3%)	0.147¥	0.6	0.35 – 1.11
	Normal	46 (60.8%)	56 (46.7%)			
Invasive Medical Devices Usage *(Central Venous Catheter)*	Yes	77 (97.5%)	114 (95%)	0.826¥	0.8	0.44 – 1.71
	No	2 (2.5%)	6 (15%)			
Mechanical Ventilator Usage	Yes	65 (82.3%)	82 (68.3%)	0.043¥*	2.1	1.07 – 4.3
	No	14 (17.7%)	38 (31.7%)			
Length-of-stay ≥ 9 days	Yes	66 (83.5%)	81 (67.5%)	0.018¥*	2.4	1.21 – 4.96
	No	13 (16.5%)	52 (26.1%)			
Antibiotic usage ≥ 7 days	Yes	35 (44.3%)	37 (30.8%)	0.074¥	1.7	0.99 – 3.21
	No	44 (55.7%)	83 (69.2%)			
Previous History of Major Surgery	Yes	17 (21.5%)	40 (33.3%)	0.100¥	0.5	0.28 – 1.05
	No	62 (78.5%)	80 (66.7%)			
Age	1 month-< 3 months old	9 (11.4%)	19 (15.8%)	0.206¥	–	–
	3 months-<3 years old	45 (57.0%)	53 (44.2%)			
	3–18 years old	25 (31.6%)	48 (40.0%)			

*Significance (p<0.05); ¥Chi Square

settings.[14]

Gram-negative bacteria are a world health problem because of their high resistance to antibiotics.[15] It is widely known that gram-negative bacteria caused 2.3 times more infection compared to gram-positive bacteria.[16] Meta-analysis studies in China show that 50% of gram-negatives are resistant to third generation of cephalosporins.[17] A 15-year cohort study in Germany showed that resistance of *E. Coli* and *K. pneumoniae* to third-generation cephalosporins increased every year, and in 2015 the rates were 16.3 and 15.7%.[18] Gram-negative bacteria were dominantly found in every specimen examined in this study. *K.pneumoniae*, *P. aeruginosa, A. baumanii,* and *E. coli* are the most commonly found. Research at Turkish Hospital also mentioned linear results with recent findings, that culture findings dominantly showed gram-negative bacteria (84.2%), with *P. aeruginosa*, *K.pneumoniae*, *A. baumanii*, and *E. coli* leading the list.[19] Previous literature from Surabaya, Indonesia revealed that in PICU setting, gram-negative bacteria were dominantly found in collected patients' specimens.[20]

K. pneumoniae is the most commonly found bacteria in this study (15%). Ranjeeta *et al*. revealed, in their meta-analysis study, that *K. pneumoniae* dominated the lab findings (16%), and 64% of them were ESBL producers.[21] Previous study located in Indonesia, Dr. Soeradji General Hospital, Klaten, revealed similar study results with 17.5% culture findings indicated for *K. pneumoniae* and 52.98% ESBL producers. The most examined isolates in previous study were sputum (40.45%),[22] which has similar numbers with recent study (55.3%). Normally, *K. pneumoniae* is easily found in the nasopharynx and digestive tract.[23] Immune-competent setting, this bacteria will never cause problems, as it is a normal flora inside of human body. However, once the immune system of host body is altered, especially in patients receiving invasive treatment such as endotracheal tubes and urinary catheters, *K. pneumoniae* poses great danger.[24] The most frequent form of complication is antibiotic resistance. Recent study found dominantly *K. pneumoniae* collected from patients with invasive treatment such as mechanical ventilators with endotracheal tubes attached to them. Colonization occurred as the result of biofilms formation at the endotracheal tube tip.[25]

Another ESBL-producing pathogens are *E. coli* with the ESBL group as much as 88.9%. This result is higher that a study conducted in a neonatal ward in China where 55% were in the ESBL-producing *E. coli* group.[26]

Similar study results were shown in a Polish national hospital.46 ESBL samples were taken for further analysis, which revealed that 43.5% of the samples were *E. coli*.[27] *E. coli* is the most commonly found bacteria in urinary tract culture samples. Turkish study reports similar findings, 73% urine isolates were dominated by gram-negative bacteria, with *E. coli* as the most commonly found bacteria.[20] *E. coli* mainly causes urinary tract infection (UTI) from both community-acquired and hospital-acquired UTI.[28] Uropathogenic *Escherichia coli* (UPEC) is the main causative agent of UTI. UPEC colonized and adheres to the urinary tract epithelium. These bacteria invade and replicate to form intracellular aggregates and cause biofilm formation. Biofilms cause bacteria to become resistant to antibiotics and host immune responses. UPEC can form biofilms on the surface of the catheter, urinary tract walls, and the epithelial lining of the bladder.[28,29]

The results of the blood isolates showed that gram positive bacteria were dominant with the most germ found were *Coagulase Negative Staphylococcus*. In line with research conducted at the PICU Hospital in Turkey from 2013–2016. 324 blood isolates were collected during the study period, 195 isolates were gram-positive (60.2%) and 107 isolates were gram-negative (33.0%). *Coagulase Negative Staphylococcus* (45.1%), *K. pneumoniae* (14.5%), *Enterococcus faecalis* (6.5%) were the most microorganisms found. This can be caused by gram-positive bacteria which are normal flora on human skin and mucosa and can contaminate blood cultures if culture specimens are not taken correctly. Gram-positive germs can also colonize and produce mucus which forms hydrophobic biofilms on medical devices such as intravenous catheters and causes infection.[30] A study in Soetomo General Hospital showed different outcomes, where the blood culture was dominated by gram-negative bacteria (66%) with *B. capea* (17.06%) as the most commonly found microorganisms. Meanwhile, gram-positive was dominated by *S. haemolyticus* (31.97%).[20]

Recent study reported that mechanical ventilators usage and prolonged length-of-stay (≥9 days) are risk factors of MDRO, sharing same results with a study by Wang *et al*.[31] who found that length of stay in the PICU, use of mechanical ventilators >5 days were risk factors for MDRO infection. A meta-analytic study also showed that a history of hospitalization within the last 3 months increases the likelihood of a carrier for antibiotic resistance.[13] The use of a mechanical ventilator which is an invasive medical procedure can remove the natural barrier of the upper airway and allow direct exposure of the lower respiratory tract to outside air, increasing the risk of colonization and invasion of bacteria in the airway epithelium.[32] Invasive procedures such as suctioning and fiberoptic bronchoscopy have been reported to increase the incidence of Ventilator-Associated Pneumonia (VAP).[31] Prolonged use of a ventilator is also associated with an increased incidence of MDR in Ventilator ventilator-associated pneumonia (VAP). One study showed that the MDR proportion of VAP patients with >5 days duration was greater (12.3%) compared to VAP patients with the duration of <4 days, namely 2.8%.[32]

Study by Qureshi *et al*[33] showed that the use of antibiotics >2 days, a stay in the ICU >3 days, and a history of using invasive medical devices (urinary catheters and CVC) are not risk factors for MDRO.[33] Another study on pediatric wards in Hospitals in Japan also showed similar results. History of administration of broad-spectrum intravenous antibiotics >2 days in 90 days, administration of short and long-term macrolide therapy (>1 month) is not a risk factor for MDR in children with pneumonia.[34] In contrast to the study by Ahmed *et al* [14] who found a significant relationship age with MDRO infection. Age <1 year is associated with an immature immune system and increased exposure to infection and environmental contamination in this study.[14] A meta-analysis study in America also showed a history of antibiotic exposure, duration of antibiotic administration, and combination antibiotics were associated with the risk of MDR occurring in pediatric patients.[35]

There was no significant difference in mortality between MDRO and non-MDRO patients. Different from previous literature results, a study conducted at the NICU Hospital in Jordan where neonatal sepsis mortality (age 0–90 days) in the MDRO group was higher than in the non-MDRO group (60% vs 13%).[36] In contrast to the study by Verma *et al*.[37] who assessed the risk factors for MDRO in children who received liver transplantation, found no significant differences between the 30-day, 90-day, and 1-year survival rates between the non-MDRO and MDRO groups.[37] Studies assessing MDRO mortality in Blood Stream Infection (BSI) in several Tertiary Hospitals in Indonesia showed the same thing. There was no difference in the risk of mortality in MDRO and non-MDRO BSI patients. This is expected due to several things such as: the use of carbapenems as empiric antibiotics can reduce the difference in risk between MDRO and non-MDRO patients, administration of empirical antibiotics without taking a culture first due to limited health insurance funding at the local hospital and the research is not specific enough to explore the differentiating factors between groups BSI MDRO and non MDRO.[38]

This study has limitations. In-depth analysis of the rationale and effectiveness for using third-generation cephalosporins as first-line empiric antibiotics in PICU setting and the analysis of factors affecting the mortality in each MDRO group has not been further elaborated in this study.

CONCLUSION

The results of this study showed that MDRO infections from various specimens were 39.7% with predominance of gram-negative germ. *K. pneumoniae* and *E. coli* as ESBL-producing bacteria had 80% and 88.9% resistance rates, respectively. Mechanical ventilators and prolonged length-of-stay are two main risk factors of MDRO in PICU setting in Dr. Kariadi General Hospital (p=0.043 and p=0.018).

Further research is needed regarding the effectiveness and rationality of using third generation cephalosporins as first-line empiric antibiotics in the PICU.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 53–57

OPEN ACCESS

Original Article

Effectiveness of Foot Exercises Together with the Hydrotherapy Program on Blood Sugar Levels in Elderly People without Diabetes

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.999

Accepted: July 05th, 2023
Approved: December 28th, 2023

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Publisher's Note:
dr. Kariadi Hospital stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract

Background : The elderly human population is susceptible to health problems due to decreased organ function. The risk of diabetes in old age also reduces quality of life. Preventing the risk of developing diabetes mellitus requires simple and simple exercise programs such as foot exercises and hydrotherapy. The effect of light leg exercise and hydrotherapy on carbohydrate metabolism is unknown. The objectives of this study was to find out the impact of hydrotherapy alone or in combination with foot exercise on elderly's blood sugar levels.

Methods : Parallel three-group pre and post-test designs for an experimental investigation. 21 elderly in RW 04 Karangwetan, Ungaran served as research participants, divided into control group (n=7), combination of foot exercises and hydrotherapy intervention group (n=7), and foot exercise intervention group (n=7). The intervention took place three times per week for five weeks. We used POCT to assess blood sugar levels.

Results : There is no significant decrease in blood sugar levels from control group ($p>0.05$). There is significant decrease in blood sugar levels from foot exercise and hydrotherapy intervention group ($p<0.05$) and foot exercise intervention group ($p<0.05$). The difference in blood sugar levels showed significant results between foot exercise and hydrotherapy intervention group and control group ($p=0.000$) and between foot exercise intervention group and control group ($p=0.004$). There is no significant differences in blood sugar levels between foot exercise and hydrotherapy intervention group and foot exercise intervention group ($p=0.112$).

Conclusion : Simple exercise activities such as foot exercises together with hydrotherapy have been proven to reduce blood sugar levels in healthy elderly populations without diabetes.

Keywords : Foot exercise, hydrotherapy, blood sugar, elderly

INTRODUCTION

The aging process will certainly have an impact on a person's health. The older the age, the more vulnerable the body is to health problems caused by decreased organ function, so proper management is needed to maintain the health of the elderly.[1] The decreased organ function causes various complaints of disease, including diabetes mellitus.[1] Diabetes mellitus is a common chronic condition among the elderly. The national diabetic prevalence rate is 10.9% based on data from the Riset Kesehatan Dasar (Riskesdas 2018). Diabetes mellitus management can be carried out with both pharmaceutical and non-pharmacological treatment. A non-pharmacological therapy can involve physical activity combined with foot exercises and hydrotherapy (soaking feet in warm water).

Foot exercises aim to enhance blood circulation, improve joint motion, and strengthen tiny muscles.[2] Foot exercise is recommended to be done with moderate intensity (with a maximum heart rate of 60–70 times per minute), for 10 minutes, 3–5 times per week for no more than 2 consecutive days without exercising.[3] In foot exercise, active muscles contracting can result in the permeability of cell membranes to increased glucose intake, reduced insulin resistance, and increased insulin sensitivity.[4] Meanwhile, sook feet in warm water with a temperature of 38–40°C above the ankles cause peripheral blood vessels to dilate in order to lower blood pressure, ease joint discomfort, and ease muscle tension, kill germs, and lower blood sugar levels.[5–7]

Therefore, this study was conducted effectiveness of the combination of foot exercise with and without hydrotherapy on blood sugar levels in the elderly.

METHODS

Three parallel pre- and post-test design methodologies were used in the experimental study with a control group during September–October 2021. The research subjects used in this study were the elderly in RW 04, Karang Wetan, West Ungaran selected by purposive sampling depending on inclusion and exclusion criteria.

(1) Ages 60 to 80 years old, (2) residence in RW 04, Karang Wetan, West Ungaran, Semarang, and (3) willingness to engage in the study by completing and signing an informed consent form are the inclusion criteria. The exclusion criteria for the research subjects were (1) unable to speak, unable to hear, unable to see, (2) unable to use and understand Indonesian, (3) had a psychiatric disorder, and (4) had a disability. The formula for an unpaired analytical research was used to calculate the sample size. The study included 21 elderly divided into three groups; control, intervention 1, and intervention 2. The determination of the subject group was carried out by a random allocation procedure. In the control group, no intervention was given. As for intervention group 1, an intervention was given in the form of foot exercises and soak feet in warm water for 5 weeks, 3 times per week.

Then, for five weeks, foot exercises were given to intervention group 2 three times each week. A video tutorial is used to perform foot exercises for foot exercises published by the Rumah Sakit Dr. Kariadi Semarang and used newspapers as materials with a duration of ±10 minutes. Then to soak feet in warm water, is done for 15 minutes with a water temperature of 40±1° Celsius which is measured using a water thermometer, and between them is given a pause for 1 minute to stabilize the water temperature to keep it warm. Measurement of blood sugar levels when carried out using Point of Care Testing (POCT) Easy Touch 3 in 1 Multi check which has been calibrated on all research subjects 2 times, prior to and following intervention.

Using the computer program IBM SPSS Statistics 25, the research data were examined. The Shapiro-Wilk test is used to determine the data's normality because there were less than 50 research participants. To evaluate the outcomes of the pre- and post-tests using normally distributed data, a paired t-test was used. One Way ANOVA with Post Hoc LSD was then used to compare the outcomes of the control group, group 1 with intervention, and group 2 with intervention.

The Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University, granted approval for the study with approval number 192/EC/KEPK/FK-UNDIP/VI/2021.

RESULTS

Characteristics of research subjects

The sample consisted of 21 elderly from West Ungaran, RW 04, Semarang. In intervention group 1, a total of seven elderly people underwent foot exercises and 5 weeks of warm water soaks. Then as many as 7 elderlies in intervention group 2 did only foot exercise intervention for 5 weeks. Table 1 presents the characteristics of the research subjects.

Comparison of blood sugar levels

A paired t-test was used to compare the blood sugar levels for each group's pre- and post-test periods based on Table 2. There were no significant differences in blood sugar levels between the pre-test and post-test in the control group, according to the findings of the various tests between pre-test and post-test, which revealed a value of $p>0.05$ ($p=0.857$). The findings of the several tests between the pre-test and post-test in intervention group 1, or the foot exercise and warm water soak group, showed $p<0.05$ ($p=0.002$), indicating that there were significant differences in blood sugar levels during the pre-test. The results of the various tests between the pre-

TABLE 1
Subjects Characteristics

Characteristics		Group			p
		Control (n=7)	Intervention 1 (n=7)	Intervention 2 (n=7)	
Age		65.57 ± 3.55;	65.43 ± 8.94;	61.71 ± 2.75;	61.71 ± 2.75;
Gender	Man	4 (57.14%)	2 (28.57%)	0 (0%)	
	Woman	3 (42.86%)	5 (71.43%)	7 (100%)	
Height		1.64 ± 0.06	1.59 ± 0.04	1.61 ± 0.04	0.211*
Weight		64 ± 6.81	64.43 ± 4.93	62.71 ± 4.35	0.831*
BMI		23.76 ± 2.18	25.35 ± 1.78	24.24 ± 1.2	0.400**

§Table Values are Mean ± Standard Deviation, *One Way ANOVA Test, **Kruskal Wallis Test

TABLE 2
Blood sugar levels of pre-test, post-test, and delta based on intervention

Group	Blood sugar levels		p	p
	Pre–test	Post–test		
Control	137.86 ± 17.01	138.14 ± 15.51	0.857¶	0.43 ± 4.12
Intervention 1	125.14 ± 24.94	113.14 ± 24.85	0.002¶*	-12.00 ± 6.30
Intervention 2	133.71 ± 15.72	125.86 ± 16.00	0.000¶*	-7.86 ± 2.80
p	0.481§	0.078§		0.000§*

*Significant (p<0.5); §One Way ANOVA; ¶Paired t

TABLE 3
Post Hoc LSD difference test between groups

Group		p	Sig.
Pre–test	Post–test		
Intervention 1	Intervention 2	0.12	Not significant
	Control	0.000	Significant
Intervention 2	Control	0.004	Significant

test and post-test in intervention group 2, or the foot exercise intervention group, then showed a p-value<0.05 (p=0.000), indicating that there were significant differences in blood sugar levels between the pre-test and post-test.

Comparison of blood sugar levels between groups
After testing the normality of the data, the difference between the pre-test and post-test scores of blood sugar levels between groups was analyzed using the One Way ANOVA test with Post Hoc LSD because the data were normally distributed. The difference between the pre-test and post-test scores in the control group was 0.43 ± 4.12. The difference between the pre-test and post-test scores in the intervention group for foot exercises and warm water foot baths was -12.00 ± 6.30. The difference between the pre-test and post-test scores in the foot exercise intervention group was -7.86 ± 2.80.

According to Table 3, there is a significant difference (p=0.000) between the pre-test and post-test blood sugar levels for the control group and the foot exercise and soak feet in warm water intervention group.

Additionally, there was a significant change in blood sugar levels between the control group and the foot exercise intervention group between the pre-test and post-test scores (p=0.004). Additionally, there was no statistically significant difference between the foot exercise intervention group and the foot exercise group in terms of blood sugar levels between pre-test and post-test (p=0.112).

DISCUSSION

The significant outcomes in the two intervention groups foot exercise plus hydrotherapy combined with exercise alone were supported by Rohani, R. earlier research from 2017, which found that foot exercise and foot soaks in warm water had a positive impact on peripheral blood circulation and reduced blood sugar levels. (p=0.002).[8] The intervention group that was given the intervention of a combination of foot exercise and hydrotherapy indicated that the results (pre-test to post-test) significantly reduced blood sugar levels were in line with previous research by Maryani, Dwi., et al in 2013 which showed that there was a significant decrease in blood sugar levels after a combination therapy intervention was performed with foot exercises and soak feet in warm water.[9]

Foot exercise is one of the physical activities that can be used as an alternative for the elderly to lower blood sugar levels. Physical activity is associated with increasing the speed of muscle glucose recovery or glucose intake used by muscles as an energy source. Muscles utilize stored glucose and when glucose is reduced, muscles will take glucose from the blood when exercising or doing physical activity. This causes a decrease in blood glucose levels and improves blood glucose control. The same thing was also stated by Stein (2001) who stated that moderate physical activity such as foot exercise can provide good benefits, such as increasing insulin sensitivity and controlling glycemia.[10]

The warm temperature of soak feet in warm water causes vasodilation of peripheral blood vessels, thereby making blood circulation smooth. Research conducted by Hoekstra SP (2008) states that soaking the feet in hot or warm water is more effective at lowering blood sugar levels than cardio exercise that requires adrenaline. Controlling blood sugar levels can help reduce risk factors for diabetes. Soak feet in warm water can burn calories up to 126 calories or the equivalent of walking for 30 minutes.[6]

The limitation of this study is that we could not control confounding variables such as the respondents' current consumption of medication, dietary habits and the composition of carbohydrates, fats and proteins, anxiety, stress levels, and previous daily physical activity. We were not optimal in collecting respondents because of the PPKM period due to Covid-19.

CONCLUSION

Elderly blood sugar levels can be reduced by physical activity, foot exercises, and hydrotherapy when done three times per week for five weeks. Which was more efficient at lowering blood sugar levels in elderly people had no discernible advantage over the other. This is demonstrated by a notable drop in blood sugar levels in both the elderly group who received a foot exercise intervention and 5 weeks of foot soaking in warm water, as well as the elderly group who just received a foot exercise intervention.

The effect of simple sports activities such as foot exercises and hydrotherapy 3 times a week for 5 weeks in elderly people without diabetes can reduce blood sugar levels. Further research on a large scale is needed to control other confounding factors.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 58–63

OPEN ACCESS

Original Article

The Relationship between the Duration of Suffering from Diabetes and HbA1c Levels with the Degree of Liver Stiffness in Type 2 Diabetes Mellitus Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1011

Accepted: August 07th, 2023
Approved: December 19th, 2023

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Publisher's Note:
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Abstract

Background : Type 2 diabetes mellitus (DM) is one of the main problems faced by the health carae system. Diabetes is a multifactorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia. Persistent hyperglycemia is associated with long-term damage to the liver. Ultrasound elastography is an imaging modality that can assess liver stiffness and can help clinicians in determining therapy, evaluating and predicting disease progression. This study aims to determine the relationship between the degree of liver stiffness using ultrasound elastography with the duration of suffering from type 2 diabetes mellitus and HbA1c levels.
Methods : This research is an observational analytic with a cross-sectional approach. This research was carried out from September 2021 to September 2022 at the radiology installation of RSUP Dr. Kariadi Semarang, then 50 research subjects were obtained who met the inclusion criteria. The Rank–Spearman correlation test was used to assess the relationship between the degree of liver stiffness and the duration of suffering from type 2 DM and HbA1c levels.
Results : The average value of liver stiffness assessed using ultrasound elastography is 7.92 ± 6.72 kPa. The average value of HbA1c levels is 8.55 ± 2.63%. The average duration of suffering from type 2 DM is 9.10 ± 6.50 years. The results of the Rank-Spearman test shows a significant relationship between HbA1c levels and the degree of liver stiffness ($p < 0.001$) with a correlation coefficient (r) of 0.68. The results of the Rank–Spearman test shows no significant relationship between the duration of suffering from type DM 2 and degree of liver stiffness ($p = 0.052$).
Conclusion : There is a relationship between liver stiffness and HbA1c levels but there is no relationship between liver stiffness and the duration of suffering from type 2 DM.

Keywords : Diabetes mellitus type 2, duration of suffering from diabetes, HbA1c level, ultrasound elastography, liver stiffness

INTRODUCTION

Diabetes mellitus (DM) is a multifactorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia. Persistent hyperglycemia is associated with long-term damage, dysfunction, and failure of the liver.[1,2] Diabetes is one of the main problems and biggest challenge faced by the health care system. Data from the International Diabetes Federation (IDF) in 2017 found that the number of diabetes sufferers in Indonesia reached 10.3 million people. The global prevalence of diabetes in adults is currently estimated at around 382 million, with 175 million undiagnosed and the greatest incidence occuring between the ages of 40 and 59 years.[3,4]

The main goal in managing diabetes therapy is to control blood sugar. High levels of HbA1c greatly influence the emergence of complications in diabetes sufferers in the form of liver damage. In theory, the long duration of suffering from diabetes mellitus is also related to the process of liver stiffness. The duration of suffering from DM is directly proportional to the risk of developing liver stiffness.[5,6]

Liver biopsy is currently considered as the gold standard for assessing liver stiffness. However, this procedure has several disadvantages involving invasive, painful, and limited to patients who are asymptomatic. In addition, the accuracy of this procedure in assessing liver stiffness can be questioned as potential for errors in sampling location and variability between examiners.[7,8]

Ultrasound elastography is an imaging modality that can be used to diagnose liver stiffness, the results of which can help clinicians in determining therapy, evaluating therapy, and predicting disease progression.[8,9] Therefore, this research was conducted to examine the relationship between the degree of liver stiffness and the duration of suffering diabetes and HbA1c levels in type 2 diabetes mellitus patients.

METHODS

This research is an observational analytical study coducted prospectively with a cross-sectional design. This study was carried out after obtaining approval from the Health Research Ethics Committee of RSUP Dr. Kariadi. Data was collected from September 2021 to September 2022 by carrying out examinations using an ultrasound elastography and medical record data from type 2 DM sufferers at Dr. RSUP. Kariadi. The sample used in this research was 50 subjects. The inclusion criteria involve type 2 DM sufferers who were over 18 years old, had an HbA1c examination and an

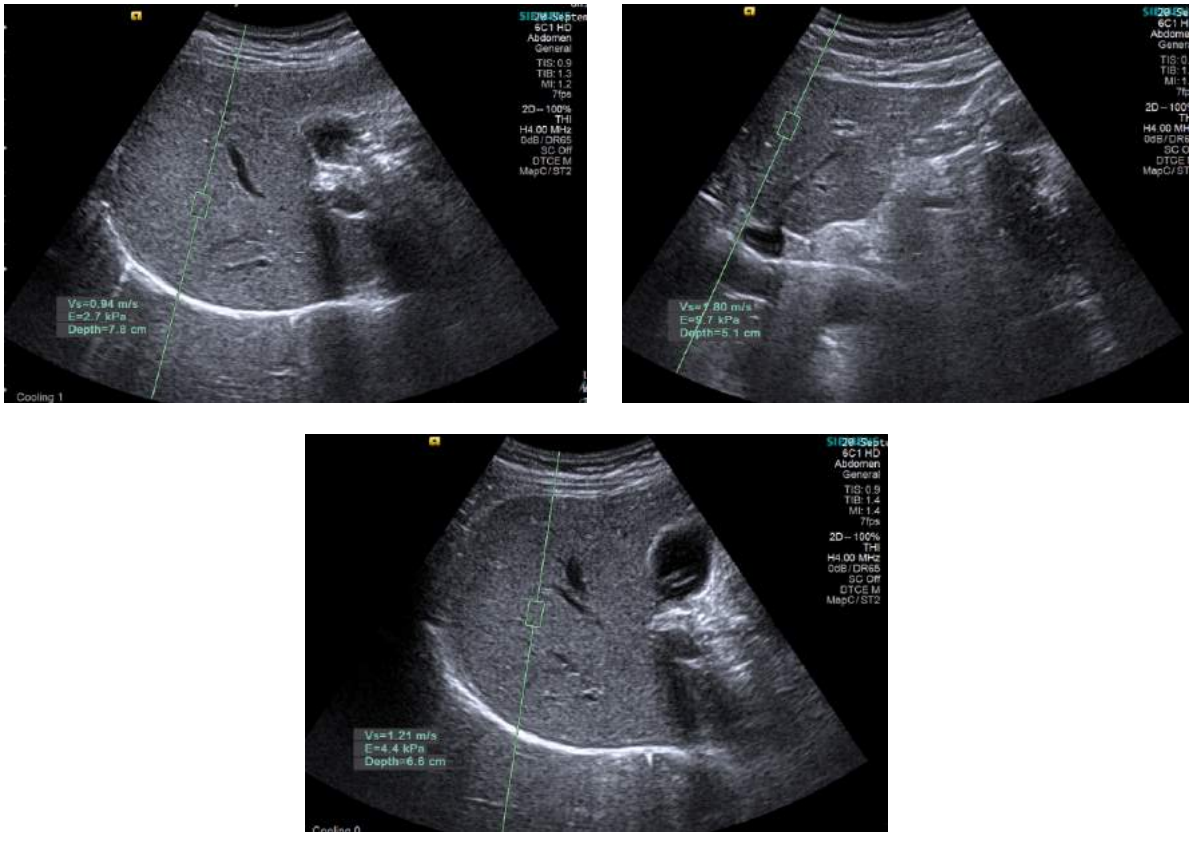

Figure 1. Elastography examination of the liver

ultrasound elastography examination. The exclusion criteria involve patients with comorbidities such as heart disease, hepatitis, biliary obstruction, liver cirrhosis, liver malignancies and alcohol-related liver disease.

This research uses Siemens Acuson S2000® ultrasound elastography. The independent variables in this study are the duration of diabetes and HbA1c levels. The dependent variable in this study is the degree of liver stiffness based on ultrasound elastography examination.

Data analysis used statistical programs consisting of descriptive analysis and statistical analysis. Descriptive analysis was carried out to examine the distribution characteristics of the number and percentage of gender, age, duration of suffering from type 2 DM, HbA1c levels and degree of liver stiffness. The Rank-Spearman correlation test was then used to assess the relationship between the degree of liver stiffness and the duration of suffering from type 2 DM and HbA1c levels.

RESULTS

Of the 50 subjects, it was found that the number of female patients is greater than male consisting of 30 (60%) female patients and 20 (40%) male patients, with a ratio of 3:2. The average age of subjects is 56.94 ± 9.28 years, the youngest patient is 40 years old and the oldest patient is 79 years old. Furthermore, the average duration of suffering from type 2 DM is 9.10 ± 6.50 years with the shortest duration of suffering from type 2 DM is 1 year while the longest duration of suffering is 27 years. The average HbA1c level is 8.55 ± 2.63%, the lowest HbA1c level is 5.5% and the highest HbA1c level is 15.8%. Examination using ultrasound elastography found the average value of liver stiffness is 7.92 ± 6.72 kPa (Table 1).

HbA1c levels are a reflection of blood glucose control in the last 10–12 weeks. Thus, HbA1c levels are a reliable parameter to reflect chronic glycemia conditions and are strongly correlated with the risk of type 2 DM-related complications, especially cardiovascular disease and stroke. HbA1c levels correlate proportionally with blood glucose levels.[11]

The examination of liver stiffness using ultrasound elastography found the majority of subjects (40%) experienced minimal fibrosis with liver stiffness values categorized at the F1: <5.7 kPa. As many as 26% patients are included in the significant fibrosis category (F2: 5.7–7.3 kPa), 20% subject are included in the cirrhosis category (F4: > 10 kPa), while the fewest number of patients is in the severe fibrosis category (F3: 7.3 – 10 kPa) involving 14% patients. The prevalence of liver stiffness is significantly higher in patients with type 2 DM. Type 2 DM is a significant risk factor for liver fibrosis in both subjects with and without liver disease.[12] Hyperglycemia is known to have a negative effect on liver cells which can initiate the progression of Non-Alcoholic Fatty Liver Disease (NAFLD) into steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis respectively. Untreated liver cirrhosis can cause irreversible cirrhosis

TABLE 1
Characteristics of research subjects based on age, duration of suffering, HbA1c levels and liver stiffness

	N	Mean	SD	Median	Min	Max
Age (years)	50	56.94	9.28	57.0	40	79
Duration of suffering DM (years)	50	9.10	6.50	8.0	1	27
HbA1c levels (%)	50	8.55	2.63	8.50	5,5	15.80
Liver stiffness (kPa)	50	7.92	6.72	6.55	2.60	14.80

TABLE 2
Characteristics of research subjects based on body weight, height, BMI and type of anti-diabetes mellitus therapies

Variable	Classification	Number	%
Body weight	< 40	0	0
	40 – 49	2	4
	50 – 59	12	24
	60 – 69	20	40
	70 – 79	10	20
	≥ 80	6	12

TABLE 2. Continued.

Variable	Classification	Number	%
Height (cm)	< 150	5	10
	150 – 159	21	42
	160 – 169	22	44
	≥ 170	4	4
IMT (Kg/m^2)	< 18.5	0	0
	18.5 – 25	19	38
	25 – 29.9	23	46
	30.0 – 34.9	7	14
	35 – 39.9	1	2
	> 40	0	0
Types of anti-diabetes mellitus therapies	Insulin, Glimepiride	8	16
	Insulin, Gliclazide	4	8
	Insulin, Glibenclamide	1	2
	Insulin, Metformin	3	6
	Insulin, Gliquidon	4	8
	Insulin	13	26
	Glimepiride, Metformin	8	16
	Gliquidon, Metformin	3	6
	Insulin, Glimepiride, Metformin	6	12

TABLE 3
Relationship between duration of suffering from DM and HbA1c levels with liver stiffness in type 2 diabetes mellitus patients

		HbA1c levels	Duration of suffering from type 2 DM
Liver stiffness	*p-value*	0,000	0,052
	Correlation coefficient	0,688	0,276

*Spearman's rank coefficient correlation test

and Hepatocellular Carcinoma (HCC) which will ultimately increase mortality.[13,14]

The subject characteristics (Table 2) show the frequency and percentage of subjects based on body weight, which is the highest number of patient's weight is in the range of 60–69 kg (40%) while the lowest number of patient's weight is in the range of 40–49 kg (4%). Based on body height, the highest number of patient's height is in the range of 160–169 cm (44%) while the lowest number of patient's height is in the range of ≥170 cm (4%). Based on Body Mass Index (BMI), the highest number patient's BMI is in the range of 25.0-29.9 Kg/m^2 (46%) while the lowest number patient's BMI is in the range of 35.0–39.9 Kg/m^2 (2%). Based on the type of anti-diabetes mellitus therapies, it was found that the highest number of patients (26%) used insulin, while the lowest of number patients (2%) used insulin and glibenclamide.

The liver stiffness value is obtained by measuring the Region of Interest (ROI) which is carried out in a neutral position as the patient is asked to take a deep breath followed by holding breath. The examination was repeated 10 times. Subsequently, the median value of the repeated examinations is used as the final result of ultrasound elastography examination presented in kilopascals (kPa).

The Kolmogorov-Smirnov test was used to determine the normal distribution of the research data. The test shows the variables of liver stiffness and duration

of suffering from type 2 DM is not normally distributed ($p < 0.05$), while the variable of HbA1c levels is normally distributed ($p \geq 0.05$), thus the statistical analysis between these variables used the Spearman's rank correlation coefficient test.

The Spearman's rank correlation coefficient test analyzed relationship between duration of suffering from DM and HbA1c levels with the degree of liver stiffness in patients with type 2 diabetes mellitus (Table 3).

The results of the Spearman's rank coefficient correlation test showed a significant correlation between HbA1c levels and the degree of liver stiffness ($p < 0.001$). The results of this study are in accordance with research conducted by Watt *et al*. (2020) on 774 Mexican–American subjects showing that HbA1c levels are parameter that have the closest relationship with liver stiffness compared with fasting glucose levels, insulin levels, and insulin resistance.[15] Apart from having a close relationship with liver stiffness, superiority HbA1c in stratifying the risk of liver stiffness also lies in the better stability of HbA1c compared to other parameters. The relationship between HbA1c and liver stiffness is also known to be unaffected by the patient's waist circumference or other confounding factors.[13,15] Similar results were also found in the study of Fernando *et al*. (2019) showing a relationship between HbA1c levels > 7% and liver fibrosis and cirrhosis.[16] In this study, the correlation shown by HbA1c levels and the degree of liver stiffness has a positive tendency (correlation coefficient of 0.688) in which increased HbA1c levels corresponds with increased degree of liver stiffness. This is in accordance with the research results of Watt *et al*. (2020) finding increased HbA1c by 10% would increase liver stiffness by 4% (positive correlation).[15] Research by Tewari *et al*. (2021) also showed positive correlation of HbA1c levels and the degree of liver stiffness with correlation coefficient of 0.820.[17]

The results of the Rank-Spearman test show no significant correlation between the duration of suffering from type 2 DM and the degree of liver stiffness ($p = 0.052$). The main goal in managing diabetes therapy is controlling blood sugar by assessing the HbA1c examination parameter. This condition will not affect the appearance of liver stiffness if HbA1c level is controlled properly regardless the duration of suffering from diabetes. This study is in contrast with previous study by Fernando *et al*. (2019) examining 121 type 2 DM patients diagnosed with NAFLD in the Philippines which found that the duration of suffering from type 2 DM for more than 5 years is related to liver fibrosis and cirrhosis.[16] Similarly, another research conducted by Tewari *et al*. (2021) shows that the duration of suffering from type 2 DM (average 10.98 years) is significantly and positively correlated with advanced fibrosis (liver stiffness >9.6 kPa) with a correlation coefficient of 0.596.[17]

CONCLUSION

There is a significant correlation between HbA1c levels and the degree of liver stiffness. The correlation shown by HbA1c levels and the degree of liver stiffness has a positive tendency with a correlation coefficient of 0.688. Secondly, there is no significant correlation between the duration of suffering from type 2 DM and the degree of liver stiffness. The main goal in managing diabetes therapy is controlling blood sugar by assessing the HbA1c examination parameter. This condition will not affect the appearance of liver stiffness if HbA1c levels is controlled properly regardless the duration of suffering from diabetes.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 64–70

OPEN ACCESS

Original Article

The Effect of Mckenzie Exercise to Increase Craniovertebral Angle in Forward Head Posture of Adolescent

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1013

Accepted: August 07th, 2023
Approved: November 29th, 2023

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Abstract

Background : Adolescents with low physical activity and smartphone addiction has been indicated to reduced the craniovertebral angle, there by causing a forward head posture and increasing scapular dyskinesis, characterized by a craniovertebral angle (CVA) less than 50o. McKenzie is one of exercise that can helm correct posture in forward head posture. This study was aimed to determine the effect of the McKenzie exercise on increasing the craniovertebral angle in the forward head posture of adolescents.
Methods : students of MAN 1 Surakarta (Islamic Boarding School) with advanced head posture, aged 14–17 years using a simple random sampling technique divided into group I as the intervention group (n=16) and group II as the control group (n=14). Group I was given treatment of McKenzie exercise 3 times a week for 4 weeks, and the control group was not given any treatment. The Craniovertebral angle were assessed using photo analysis with Image-J application.
Results : The results of the study indicate that the characteristics of respondents according to age are mostly 16 years old. The mean NDI score in the intervention group was 23.63 and the mean NDI score in the control group was 24.60. The results of statistical test using independent samples test showed that there was a significant difference during the intervention and the control group (p=0.000)
Conclusion : McKenzie's exercise can affect to increasing the craniovertebral angle in the forward head posture of adolescents.

Keywords : forward head posture; McKenzie exercise; craniovertebral angle

INTRODUCTION

Posture is defined as a position or attitude of the body, the relative arrangement of body parts for a specific activity. Forward head posture isi characterized by increased felxion of the lower cervical spine and upper thoracic region and increased extension of the upper cervical spine.[1] Bad posture is a serious health problem which causes more musculoskeletal disoreder. An adolescent inculcate the habbit of forward neck posture at a very early age due to studiying in various odd positions. Inadequate posture consists of poor interrelations between parts of the body. These imperfect interrelations cause muscle tension and shortening, which make appropriate joint movements more difficult to achieve and my cause pain.[2]

Low physical activity in adolescents due to static body position when sitting in class during 4–7 hours of school learning activities with school furniture that does not match body dimensions, such as the table height is too short,[3,4] and learning activities in dormitories, such as recite in a static position for ≥2 hours, can cause changes in neck and shoulder posture. The change in posture is the forward head posture.

Forward head posture is characterized by the position of the head relative to the front of the cervical vertebrae in the sagittal plane. Forward head posture is associated with upper cervical vertebrae hyperextension (C1–C3) and lower cervical vertebrae flexion (C4–C7).[5] Adolescents who experience forward head posture for a long time cause damage to the muscles, and bone structure, and changes in the body's functional abilities. Therefore, to determine the forward head posture in adolescents, measurements are made by assessing the angle using the craniovertebral angle (CVA) (Figure 1). CVA measurement results ≤50° are a sign of a forward head posture.[6,7] The tool used to get the angles of the forward head posture is the Image-J application by analyzing the images in the sagittal section.

Forward head posture in adolescents can be given appropriate interventions to increase craniovertebral angle by using McKenzie exercise. Mckenzie exercise is a self-therapeutic, repetitive exercise, focused on extension.[8] In addition, it can improve function of patients, reduce recurrence pain, and associated stress. Therefore it can provide posture correction in forward head posture and help improve alignment or alignment in the neck.[9,10]

Understanding forward head posture and related functional changes can help early detection of forward head posture in adolescents, can then determine more appropriate intervention strategies at once, and increase awareness of the need for early intervention.

Therefore, the purpose of the present study was to investigate the effects of McKenzie exercise to increase craniovertebral angle in forward head posture.

METHODS

Study design

This study to determine the effect of McKenzie exercise to increase craniovertebral angle in forward head posture of senior high school adolescents. Subjects were randomly assigned to the experiment group and control group by selecting one of two cards from a box. The participants were not informed of the research hypothesis, and the evaluator was blinded. The subjects in the experimental group underwent McKenzie exercise, whereas the control group received no intervention. This study was approved by the health research ethics committee RSUD Dr. Moewardi. This study has been registered in the number of ethical clearance 1.041/VIII/HREC/2022.

Subjects

In this study, 30 participants with forward head posture were recruited in the boarding school program MAN 1 Surakarta from August to November 2022 The following inclusion criteria were applied: students aged

Figure 1. Craniovertebral angle landmark

Figure 2

Figure 3

Figure 4

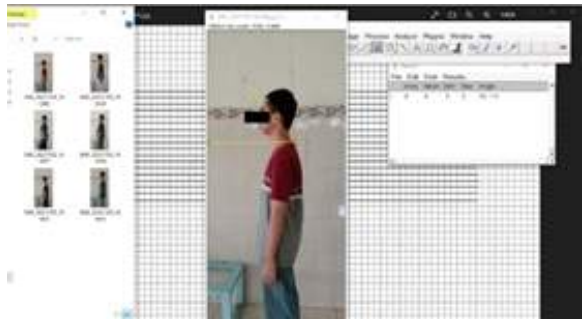

Figure 5

14–17 years, forward head posture with a CVA value of ≤50°, neck disability index or NDI value of <28% (mild disability) which is a 10-item questionnaire that measures a patient's self-reported neck pain related disability, the questions include activities of daily living, such as: personal care, lifting, reading, work, driving, sleeping, recreational activities, pain intensity, concentration and headache, willing to take part in the exercise program and sign an informed consent. Participants were excluded if they presented: history of vascular disorders (vertigo), history of injuries vertebral column and upper extremities which made it impossible to perform exercises such as fractures and dislocations, history of surgery on the vertebral column and upper extremities, history of inflammatory disease, presence of tumors in the vertebral column, history of postural congenital disorders. Participants were dropped out if they presented: subjects who did not take part in the exercise more than three times, and subjects who did not take part in the post-test.

Examination procedures

All participants were measured using the craniovertebral angle (CVA). The craniovertebral angle is the acute angle formed between the horizontal line passing through the C7 spinous processes and the line connecting the midpoint of the tragus to the C7 spinous processes.[6,7]

The CVA measurement procedure begins with preparation for measurement, by placing the camera perpendicular to the ground using a tripod and oriented camera lens in the sagittal plane as far as 80 cm.[7,11] Then, prepare for the individual's position standing comfortably in front of a plain wall and looking straight ahead. Next, palpate the midpoint of the tragus and C7 spinous process and attach a sponge mark, then take a sagittal photo of the body. Next, the photos were analyzed using the Image-J application.[7,11]

The CVA measurement results which indicate a forward head posture is ≤50° or the smaller the degree of CVA results, it can indicate a forward head posture.[6,7,9]

Intervention

McKenzie's exercises were carried out in the experimental group 3 times a week for 4 weeks, 10 repetitions for 2 sets, by maintaining the movement position for 7 seconds and resting for 3 seconds before returning to the starting position. McKenzie's exercises included head retraction with overpressure while sitting, neck extension while sitting, head retraction with overpressure while lying, side bending of the neck while sitting, neck rotation while sitting, neck flexion with chin-n in the sitting position.

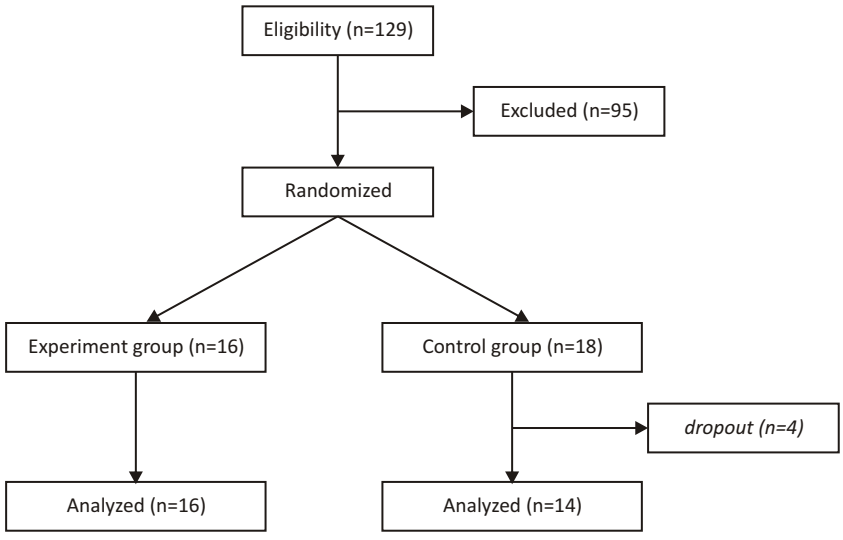

Figure 6. Flowchart of the recruitment, randomization, and follow-up of participants

TABLE 1
Baseline characteristic for the two groups

Characteristics		Experiment group (n=16)	Control group (n=14)	*p value*
Age*		16.00 ± 0.730	15.71 ± 0.726	0.293
Age (years)	15	4 (25%)	6 (42.86%)	
	16	8 (50%)	6 (42.86%)	
	17	4 (25%)	2 (14.28%)	
Gender	Male	6 (37.5%)	5 (35.71%)	0.923
	Female	10 (62.5%)	9 (64.29%)	
NDI*		23.63 ± 2.88	24.60 ± 2.54	0.618

*Mean ± standard deviation

TABLE 2
Comparisons of between-group change scores for CVA

Variable	Experiment group (n=16)				Control group (n=14)				Comparisons	
	Pre-test	Post-test	Pre post-test	*p value*	Pre-test	Post-test	Pre post-test	*p value*	Pre post-test Mean difference (95% CI)	*p value*
CVA*	50.09 ± 0.28	58.21 ± 4.78	8.11 ± 4.71	0.000	49.68 ± 0.64	50.40 ± 2.96	7.18 ± 2.72	0.342	7.80 ± (4.77 – 10.83)	0.000

*Mean ± standard deviation

Data analysis

The baseline characteristics of participants were compared between treatment groups, using independent t tests to assess the adequacy of the randomization (Table 1). The effects of interventions on CVA was examined by using a paired sample t-test, and CVA for between groups were compared using an independent t test. Data analysis was conducted using SPSS 26.0 version (IBM, Chicago, IL, USA) statistical software for Windows.

RESULTS

Based on the results of this study, 30 out of 168 students were found to have forward head posture and showed no differences in the characteristics of the research subjects between the experimental group and the control group, as shown in Table 1. In each of these study groups the dominance of the age of the research subjects was 16 years, and female sex dominated, namely 62.5% in the experimental group and 64.29% in the control group. Next, the characteristics of the research subjects based on the NDI in each group showed that the maximum NDI was 26.60%, in the mild disability category.

In the experimental group with 16 subjects, the results of the pre-test and post-test were different, p = 0.000, Table 2. The results of the paired sample t-test in the experimental group showed a p value <0.05, which means there was a significant difference. While the results of the pre-test and post-test differences in the experimental group with 14 research subjects obtained p = 0.342. The results of the experimental group's paired sample t-test showed a value of p <0.05, which means there was no significant difference. Furthermore, the post-test difference test between the experimental and experimental groups used the independent t-test, the results obtained were p=0.023, indicating p<0.05 meaning there was a significant difference.

DISCUSSION

The results of this study are in accordance with the results of previous studies which demonstrated the efficacy of McKenzie exercise on forward head posture.[9,12] Recent research shows that results suggest that the combination of upper thoracic mobilization and mobility exercise may provide short-term benefits to individuals with FHP.[13]

Furthermore, the results of this study show that the dominance of the age of the study subjects is 16 years, and the female sex predominates compared to the male. The chances of forward head posture occurring are more in the teenage years due to low physical activity, static body position while sitting in class during learning activities at school 4–7 hours and school furniture that does not match body dimensions,[3,4] as well as learning activities in dormitories in a static position for ≥2 hours. Furthermore, the predominance of the female sex in each group is twice as high as that of males, because females have been identified as having 2°–3° more neck flexion than males.[14,15] This is related to psychosocial problems such as stress which are partly related to secondary sexual characteristics.[16] The results of this study were similar to those found in previous studies, such as research study on 275 adolescents aged 15–17 years who reported that forward head posture and rounded shoulder postural malalignment were the most common postural disorders, especially in female adolescents (n = 153).[14] Then the results of research on 189 research subjects (12–16 years) suggested that a greater percentage of female students (71.1%) experienced forward head posture when compared to male students (55.7%).[17] Next, the characteristics of the research subjects based on the NDI in each group showed that the maximum NDI was 26.60%, in the mild disability category. The research subjects answered 9 out of 10 question sessions on the NDI questionnaire sheet. In the 8th question session (driving) was not answered because the research subjects were dormitory students and female students who did not use vehicles to go to school. According to research found a relationship between forward head posture and disability.[18]

Based on the results of this study, McKenzie exercise had an effect on increasing the craniovertebral angle in the forward head posture of high school adolescents, as evidenced by the significant increase in CVA in group I (p=0.000). There was a significant increase in CVA in group I because adolescents who experienced forward head posture had abnormally activated muscles, shortening of the deep cervical flexor and lengthening of deep cervical extensor which resulted in a class 1 lever system in the cervical vertebral region, axis position (A) which is closer to resistance (R).[19] Changes in the lever system 1 in the cervical region can cause a shift in the center of gravity (COG) to the anterior. The upper body will move backwards and the shoulders will move forward to compensate for this shift, so that the head will be more anterior than the vertebrae.[20]

McKenzie exercise has the goal of activating the deep cervical flexor and deep cervical extensor muscles normally.[10,13] The synergy of activated muscles will generate strong impulses in the muscle spindles and golgi tendon organs. The muscle spindles and the golgi tendon organs work together to control and detect all tension during muscle contraction. Muscle spindles work to maintain constant muscle length by providing feedback on changes in contraction, where the muscle spindle plays a role in stopping nerve impulses that increase tension in the antagonist muscles to prevent overstretching. This event results in relaxation of the antagonist muscles, or is called reciprocal inhibition. Meanwhile, sensory nerve impulses from the Golgi tendon organs enter the dorsal portion of the spinal cord

and encounter inhibitory motor neurons. This process prevents further agonist muscle contraction from occurring, accompanied by a decrease in muscle tone, resulting in relaxation of the agonist muscle, known as post isometric relaxation.[10]

The McKenzie exercise carried out in this study uses repetitive movements which include mobilization and manipulation, and focuses on stretching exercise at each stage. The dose of McKenzie exercise in the group I used was 10 repetitions of 2 sets, by maintaining the movement position for 7 seconds and 3 seconds of rest before returning to the starting position. The total exercise is done 3 times a week for 4 weeks. This dosage refers to the results of research which can increase the CVA value in forward head posture in the McKenzie exercise treatment group.[9,12]

Cyclical stretching through stretching force is done repeatedly using several repetitions during one therapy session and each movement is maintained for 5–10 seconds can help increase muscle flexibility. Also, if an exercise program is in the form of stretching exercises using a frequency of exercises carried out at least 2 times per week, it can increase the mobility of joint motion.[21]

Proportionally balanced movement through McKenzie exercise can improve proprioception improvement in muscles, tendons, joints and connective tissue around the neck, upper back and shoulders. Thus, it can provide a strengthening and stabilizing effect on agonist and antagonist muscle groups, which directly helps posture correction in forward head posture .[10]

Posture correction in forward head posture through McKenzie exercise can increase the value of craniovertebral angle, it is proven from the results of this study that indications of adolescents with forward head posture have a CVA value of ≤50°, after group I was given McKenzie exercise there was an increase of CVA Value at >50°, as shown in Table 2. If there is an increase in the CVA value, the severity of forward head posture decreases and can increase the body's functional activities.[9,10]

CONCLUSION

McKenzie's exercise affects increasing the craniovertebral angle in the forward head posture of high school adolescents, which can be achieved if it is done consistently according to the prescribed dosages of exercise, daily activities, and has a motivational exercise goal. Accordingly, senior high school adolescents with forward head posture can carry out their daily activities without obstacles or complaints. Future studies should examine the effectiveness of different types and dosages of manual therapy, and perform long-term follow-up data collection.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 71–78

OPEN ACCESS

Original Article

Effectiveness of Kelly Plication Method on Clinical Improvement in Stress Urinary Incontinence Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1032

Accepted: October 02th, 2023
Approved: December 19th, 2023

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Abstract

Background : Patients with pelvic organ prolapse (POP) usually present with POP, but stress urinary incontinence (SUI) is also found during history taking and physical examination. As a result, the complaint of SUI is persistent despite POP surgery. Therefore, SUI found along with POP and undergoing surgery can be performed Kelly plication method. The objectives ot this study was to examine the effectiveness of Kelly's plication method on clinical changes and quality of life of patients suffering from SUI.
Methods : A single cohort prospective one-group pretest-posttest design conducted at RSUP Dr. Kariadi Teaching Hospital Semarang involving 31 research subjects. All subjects were measured preoperative IIQ-7 questionnaire and pad test. Then, all subjects will undergo Kelly method surgery. Postoperative evaluation will be conducted 3 months later, including measurement of the IIQ-7 questionnaire and pad test. All data will be analyzed with univariate and bivariate analysis using paired t-test and Wilcoxon test.
Results : The effectiveness rate of Kelly's plication method was 58.06% in this study. Most of the subjects were aged 50–59 (38.7%) years and had experienced menopause (87.1%). Correlation analysis of baseline data on the degree of preoperative SUI showed that the degree of POP correlated SUI. The Pad test and IIQ-7 questionnaire test showed a significant decrease in postoperative measurements in the treatment group ($p < 0.001$ & $p < 0.001$).
Conclusion : Kelly's plication method is effective in treating SUI.

Keywords : stress urinary incontinence, SUI, Kelly plication, pelvic organ prolapse.

INTRODUCTION

According to the definition by the International Continence Society (ICS), urinary incontinence is a complaint of involuntary urine loss that is objectively demonstrable and is a social or hygiene problem.[1,2] Elderly women are most commonly affected by stress urinary incontinence (SUI). In Indonesia, the overall prevalence of urinary incontinence ranges from 23–35%, with stress urinary incontinence accounting for 17.9% of cases.[3,4] Despite often being overlooked by patients and their families, stress urinary incontinence (SUI) can reduce the quality of life and productivity of those affected. Moreover, individuals with SUI may experience external genital irritation or even urinary tract infections as a result of infrequently changing sanitary pads.[5] Although patients with pelvic organ prolapse (POP) typically present with POP-related complaints, stress urinary incontinence (SUI) is often discovered during the medical history and physical examination. Consequently, SUI symptoms may reoccur after POP reconstruction surgery. Occult Stress Urinary Incontinence (OSUI) refers to hidden SUI that occurs after reconstruction in patients with pelvic organ prolapse (POP). The prevalence rate of OSUI in women with severe POP is estimated to range between 27% until 68%.[6]

The management options for patients with SUI can be categorized into non-operative therapy and operative therapy.[7] Non-operative therapy can be further divided into pharmacological and non-pharmacological therapy. Non-pharmacological therapy may include lifestyle modifications such as reducing caffeine intake and weight loss, Kegel exercises to strengthen pelvic floor muscles, or the use of a pessary for patients with SUI.[7] Invasive treatment options for managing SUI include neuromodulation, Kelly plication, Burch colposuspension surgery, the retropubic urethropexy methods such as Raz or Marshall-Marchetti-Krantz, or sling placement surgeries like transobturator tape (TOT) and tension-free transvaginal tape (TVT).[8] In both of these methods, a sling is placed as a substitute for the pubourethral ligaments.[9] These surgical methods are quite expensive and may not be covered by the Indonesian National Health Insurance (Jaminan Kesehatan Nasional or JKN). Therefore, for patients with concurrent stress urinary incontinence and pelvic organ prolapse who undergo surgery, the Kelly plication method is often chosen as it is more cost-effective. The aim of this study is to assess the effectiveness of the Kelly plication method in terms of clinical improvement and quality of life for patients with stress urinary incontinence in Indonesia, addressing the lack of available data on its efficacy.

METHODS

The research was conducted using an observational analytical method with a single cohort prospective design, one-group pretest-posttest. It took place over a period of one year, from December 2021 to December 2022, at the Obstetrics and Gynecology Clinic of Merpati Polyclinic RSUP Dr. Kariadi, a teaching hospital in Semarang. This study obtained ethical clearance from the Medical Research Ethics Commission of the Dr. Kariadi Central General Hospital Semarang with approval number: 948/EC/KEPK-RSDK/2021.

Consecutive sampling of 31 samples who were willing to take part in this research and undergoing surgery were included in this study. Patients with a history of uncontrolled diabetes mellitus, a body mass index (BMI) greater than 40 kg/m^2, pregnancy, malignancies, hormonal estrogen therapy, a history of stroke, smoking, and regular alcohol consumption were excluded as criteria for this research sample.

Subsequently, individuals who were willing to participate in the study, including their readiness to undergo the surgical procedure, were provided with an explanation, research information sheet, and research consent letter outlining the research's conduct, objectives, procedures, benefits, risk, disadvantages and expected outcomes. Patient data include name, date of birth, weight and height, occupation, address, and last education were then retrieved from their medical records, and a validated Indonesian version of the IIQ-7 questionnaire was administered to the patients through a structured interview conducted by the researcher or research assistant. The IIQ-7 questionnaire were a tool to assess life quality and symptom distress for urinary incontinence (UI) in women. Patients were then admitted for preoperative preparation. Following this, the Kelly plication surgical procedure was performed by multiple healthcare professionals as a treatment for UI based on medical indications. Three months post-operation, subjects who had undergone the surgical procedure completed the IIQ-7 questionnaire through a structured interview, and pad tests were conducted both before and after the operation. A three-month analysis were carried out since there should be improvement in complaints and asses the effectiveness of short-term actions.

Univariate analysis was used to present the characteristics of the study subjects by providing the distribution of variables using descriptive statistics such as mean, median, and standard deviation. Tables displayed quantitative data. Paired T-tests were conducted to analyze the pad test and IIQ-7 questionnaire results before and 3 months after the operation. The significance level was set at $p<0.05$. The Wilcoxon test was used for non-normally distributed data.

RESULTS

The total number of patients with stress urinary incontinence who presented at the Obstetrics and Gynecology Clinic of Merpati Polyclinic RSUP Dr. Kariadi during the study duration was 40 patients. Five patients declined to participate in the study, while 2 patients had morbid obesity (BMI >40 kg/m^2), and 2 patients had type 2 diabetes mellitus, leading to their exclusion from the study. This resulted in 31 patients who met the inclusion criteria and provided informed consent to participate in the research.

Characteristics of Study Subjects

The largest age group in the study was between 50–59 years old (n=12, 38.7%), with an average age of 59.58 ± 8.64 years. All research subjects were married, with only 3 subjects having been married twice. A total of 27 subjects (87.1%) involved in the study had experienced menopause, with an average duration of 10.52 years. In this study, all subjects were married, and among them, 22 patients (71.0%) had a history of giving birth more than two times, with vaginal deliveries being the most common (n=30, 96.8%). The majority of the research subjects had a normal BMI (n=14, 45.2%).

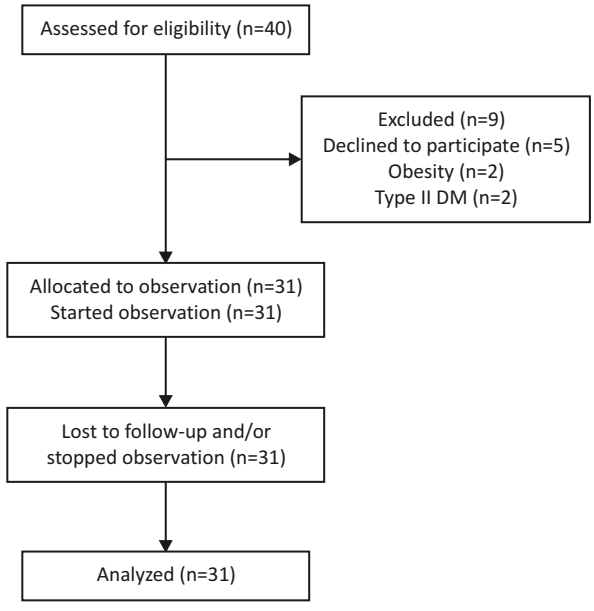

Figure 1. Consort Diagram

TABLE 1
Research Subject Characteristics

Variable		n	%	Mean ± SD	Median (min – max)
Age	40 – 49 years	5	16.1	59.58 ± 8.64	58 (42 – 72)
	50 – 59 years	12	38.7		
	60 – 69 years	10	32.3		
	≥ 70 years	4	12.9		
Parity	1 – 2	9	29.0		
	> 2	22	71.0		
Delivery	Caesar Section	1	3.2		
	Vaginal Birth	30	96.8		
Menopause	No	4	12.9		
	Yes	27	87.1		

TABLE 1. Continued.

Variable		n	%	Mean ± SD	Median (min – max)
Menopause duration				10.52 ± 6.49	10 (2 – 21)
BMI	Underweight	1	3.2		
	Normal	14	45.2		
	Overweight	11	35.5		
	Obesities I	5	16.1		
POP Degree	Mild	5	16.1		
	Severe	26	83.9		
Preoperative SUI	Mild	9	29		
	Moderate	17	54.8		
	Severe	5	16.1		

TABLE 2
Analysis of the Differences in the Characteristics of Study Subjects by Preoperative SUI Severity

Variable		SUI pre op			p
		Mild	Moderate	Severe	
Age	40 – 49 years	2 (22.2)	2 (11.8)	1 (20)	0.817£
	50 – 59 years	3 (33.3)	7 (41.2)	2 (40)	
	60 – 69 years	2 (22.2)	7 (41.2)	1 (20)	
	≥70 years	2 (22.2)	1 (5.9)	1 (20)	
Parity	1 – 2	2 (22.2)	5 (29.4)	2 (40)	0.780£
	>2	7 (77.8)	12 (70.6)	3 (60)	
Delivery	Caesar Section	0 (0)	1 (5.9)	0 (0)	0.653£
	Vaginal Birth	9 (100)	16 (94.1)	5 (100)	
Menopause	No	2 (22.2)	2 (11.8)	0 (0)	0.483£
	Yes	7 (77.8)	15 (88.2)	5 (100)	
Menopause duration		10.4 ± 7.2	11.2 ± 6.5	8.6 ± 6.5	0.770¥
BMI	Underweight	0 (0)	1 (5.9)	0 (0)	0.408£
	Normal	6 (66.7)	5 (29.4)	3 (60)	
	Overweight	1 (11.1)	8 (47.1)	2 (40)	
	Obesities I	2 (22.2)	3 (17.6)	0 (0)	
POP Degree	Mild	4 (44.4)	0 (0)	1 (20)	0.013£*
	Severe	5 (55.6)	17 (100)	4 (80)	

*Significant (p <0.05); £ Chi–Square; ¥ Spearman's Correlation

All study subjects were UI patients with pelvic organ prolapse who underwent pelvic organ reconstruction procedures, including anterior colporrhaphy, simultaneously with the Kelly plication method. Pad test examinations and completion of the IIQ-7 questionnaire were conducted prior to the surgical procedure. Subjects underwent the second evaluation of these examinations three months after the operation.

TABLE 3
Results of the Wilcoxon test for the pad test

Pad Test (gram)	Mean ± SD	Median (min – max)	p
Preoperative	25.56 ± 18.24	19.20 (3,00 – 63.00)	<0.001‡*
3 months postoperatively	3.73 ± 2.84	3.20 (0,30 – 11.30)	

*Significant; ‡Wilcoxon-test (p <0.05)

TABLE 4
Results of the paired t-test for the IIQ-7 questionnaire

IIQ-7 Questionnare (score)	Mean ± SD	Median (min – max)	p
Preoperative	53.75 ± 21.02	57.10 (14.28 – 95.23)	<0.001+*
3 months postoperatively	10.60 ± 10.04	9.52 (0.00 – 38.09)	

+Paired t-test (p <0.05); *Significant

TABLE 5
Effectiveness of the Kelly Plication Method

Preoperative	Postoperative				Total
	Severe	Moderate	Mild	Fully-Recovered	
Severe	0	1	0	4	5
Moderate	0	0	10	7	17
Mild	0	0	2	7	9
Total	0	1	12	18	31

The degree of POP has an influence on the severity of UI (p=0.013), whereas age, parity, mode of delivery, menopause, and BMI do not have a significant impact on the occurrence of UI.

Pad Test

According to the pad test examination, the median value before treatment was 25,56 ± 18,24, with a range of 0,03 to 11,30 after treatment. The Wilcoxon test was employed because the research data did not follow a normal distribution. The results indicate a significant difference in the mean values of the pad test before and three months after Kelly plication. The study assessed the therapy's success based on daily pad usage. Therapy was considered successful if patients did not use pads six months after the operation. The Kelly plication group exhibited a significant decrease in the number of pads used before and after the surgery.It was found that there was a significant decrease in pad test results before the operation compared to 3 months after the operation, with a difference of 21.83 ± 15.4 grams.

IIQ-7 Questionnare

To assess quality of life scores, the IIQ-7 questionnaire was utilized. The mean score on the questionnaire before Kelly plication was 53.75 ± 21.02, while the score 3 months after the operation was 10.60 ± 10.04. A paired t-test was employed to assess significance due to the normally distributed data in the study. The results of the paired t-test show a statistically significant difference in the mean scores of the IIQ-7 questionnaire when comparing before and three months after the Kelly plication procedure.

Kelly Plication Effectiveness

At the outset of the study, 31 subjects were experiencing UI. Following the Kelly plication procedure, clinical evaluation was continued, with a pad test indicator performed three months after the surgery, revealing that 13 patients still experienced UI. Consequently, the success rate of Kelly plication in UI patients was 58.06%.

The study assessed the therapy's success based on daily pad usage. Therapy was considered successful if

patients did not use pads six months after the operation. The Kelly plication group exhibited a significant decrease in the number of pads used before and after the surgery, namely, 1.92 ± 0.95 vs. 0.4 ± 0.12 (p=0.001).[18] Similar to this study, it was found that there was a significant decrease in pad test results before the operation compared to 3 months after the operation, with a difference of 21.83 ± 15.4 grams.

DISCUSSION

The Kelly plication method is a surgical procedure for the correction of anterior vaginal defects, aiming to reinforce the pubovesical fascia around the bladder neck and proximal urethra to provide necessary support and aid in the mechanism of urethral sphincter closure, thereby preventing urinary leakage. This study represents an observational analytical study with a pre-test and post-test design within a single group, prospectively conducted on 31 SUI patients concurrently diagnosed with POP, who presented at the Obstetrics and Gynecology Clinic of Merpati Polyclinic RSUP Dr. Kariadi, Semarang. All subjects in the study underwent pelvic organ prolapse reconstruction surgery along with Kelly plication.

The peak incidence of UI in women occurs at the age of 50. In this study, the mean age of women experiencing UI was 59.58 ± 8.64 years, with the youngest being 49 years old and the oldest being 72 years old. The majority of UI cases occurred in the age group of 50–59 years (n = 12, 38.7%). In this study, age did not have a significant influence on the occurrence of UI, consistent with a study conducted in Taiyuan.[10] Findings from a study conducted in Saudi Arabia indicate that UI occurs most frequently in the age range of 50–59 years.[11] The results of this study differ from research conducted on 236 Indian women, which reported that age influences the prevalence of UI in women, with 60% of UI cases occurring in the age group above 50 years.[12] This study found that 87% of the patients had experienced menopause with an average duration of menopause of 10.52 ± 6.49 years, although it did not have a statistically significant impact on the occurrence of UI. These results can be explained by the article by Gabriela, where SUI in menopausal patients is not influenced by the duration of menopause, but mainly by the number of pregnancy and births, the baby's birth weight, the patient's BMI, and the patient's chronic conditions.[13]

In this study, 22 subjects (71.0%) had a parity status of more than 2 times, while 9 subjects (29.0%) had a parity status of 1 or 2 times. However, the results of this study were not statistically significant. These results are supported by previous meta-analysis study by Zhou that concluded higher parity has a more significant effect on overall UI, but it all depends on the chronic condition of each patient. The article found that pregnancy and childbirth, especially in multiparous women, were correlated with an increased prevalence of UI. It is known that women who gave birth 1, 2, and more than 3 times had a risk of 1.43 [95% CI: 0.90–2.28; I2=81.4%; n=4], 1.50 (95% CI: 1.02–2.20; I2= 82.5%; n=4), and 1.58 (95% CI: 1.22–2.03; I2=70.1%; n=7), respectively. The study found that having a parity status of more than 2 had the potential to increase the risk of UI compared to nulliparity.[10,14] There is a possibility that this is due to trauma that occurs to the connective tissue or pelvic floor muscles during the childbirth process, which can disrupt bladder function. Based on this hypothesis, the method of childbirth also influences the risk of UI. It was found that cesarean section delivery did not correlate with the risk of UI, whereas vaginal delivery with instrumentation doubled the risk of UI compared to cesarean section delivery. Only 1 subject (29.0%) had a history of cesarean section delivery, and 30 subjects (96.8%) had a history of vaginal delivery, aligning with the characteristics of the study subjects' data.[15,16]

Before the Kelly plication procedure, all study subjects underwent a pad test. This test can be used to determine whether there are changes in incontinence before and after the Kelly plication. The results of the pad test before the surgery had an average of 25.56 ± 18.24 grams, with the smallest result being 3 grams and the highest 63 grams. This wide range of results was influenced by the severity of pelvic organ prolapse (POP) present, where severe POP, namely, stage 3 and stage 4, had significance in increasing the occurrence of UI (p=0.013). The association between POP and UI is based on the shared pathophysiology between the two, involving damage to the ligaments in the pelvic area, as well as similarities in intrinsic predisposing factors such as genetics, race, menopause, and extrinsic predisposing factors including obstetric history, prior pelvic surgeries, obesity, and underlying comorbid diseases.[17]

To assess the effectiveness of the surgery, a repeat pad test examination was conducted during the three-month post-Kelly plication follow-up visit. The results of the pad test at three months post-Kelly plication were lower than those obtained before the surgery. This three-month observation serves as a short-term follow-up. In addition to assessing effectiveness, this short-term observation within a three-month timeframe is performed to evaluate the safety of the procedure and to identify any adverse events associated with the Kelly plication method.[18] A study conducted in Brazil observed the effects of vaginal hysterectomy with the addition of Kelly plication compared to the addition of TOT in POP patients with UI.

One of the instruments used to assess the quality of life of patients following urinary incontinence surgery is the IIQ-7 questionnaire. In a study involving the treatment of UI patients who underwent anterior colporrhaphy with the addition of Kelly plication,

a reduction in IIQ-7 scores was observed before [median 5 (1–10)] and 13.5 years after the procedure [median 0 (0–1)] (p=0.0435).[20] Similar results were also found in another study involving patients with a BMI less than 30 and those with a BMI greater than 30 who underwent mid-urethral sling techniques such as TVT or TOT. In both obese and non-obese women, the IIQ-7 scores decreased before the surgery and 12 months after the surgery (0.0, 95% CI 0.0–4.8 versus 0.0, 95% CI 0.0–14.3, p= 0.033).[21]

The results of the pad test evaluation conducted within 60 minutes indicate that patients are considered cured if the pad test result is less than 3 grams. This study reported a success rate of 58.06% for the Kelly plication procedure. The success rate reported in this study is notably lower in comparison to earlier literature, which indicated therapy success rates of approximately 80% at the three-month evaluation, 63% at the one-year evaluation, and 37% at the five-year evaluation following surgery. The results of this study highlight a lower success rate for the Kelly plication procedure in the short term. However, it's important to note that this research only had a three-month follow-up period. Therefore, longer-term symptom monitoring is needed to assess the effectiveness of Kelly plication in clinical outcomes for UTI patients. Another limitation of this study is that it included only one group of subjects who underwent Kelly plication, without a control or comparative group with other surgical procedures like TVT, TOT, and TVT-O. Despite these limitations, it's noteworthy that significant improvements in patients' quality of life and positive outcomes in the pad test results were observed, contrasting with historical literature. These results indicate that the low success rate value is mainly caused by the shorter follow-up time compared to previous studies, where there is no 1 years and 5 years follow up. This is supported by the value of quality of life and pad test results which are not inferior to previous research. It is essential to interpret these findings in the context of the evolving landscape of UI management and to consider factors contributing to this discrepancy. Further research with extended follow-up periods and larger, diverse subject populations may provide a more comprehensive understanding of the long-term efficacy of the Kelly plication method in UI patients. These findings underscore the importance of ongoing research to refine treatment strategies and optimize outcomes for UI patients.[22] Another study comparing Kelly plication and TOT reported a success rate of 64% for the Kelly plication six months after the procedure, in contrast to a success rate of 68% for TOT.[19]

Limitations

This study had a limited three-month follow-up period, necessitating the monitoring of symptoms in both the medium term (between 3–12 months post-operation) and the long term (beyond 12 months) to assess potential reductions in the effectiveness of the Kelly plication method on clinical changes in UI patients. Another limitation of this research is its exclusive focus on a single group of subjects undergoing Kelly plication, without a comparative group subjected to alternative surgical procedures such as TVT, TOT, and TVT-O. Furthermore, the distribution of subjects across the various severity levels of UI within this study was not uniform.

Nonetheless, the strength of this study lies in its attempt to quantitatively analyze the effectiveness of the Kelly plication method based on urinary pad test results and qualitatively based on the IIQ-7 questionnaire. These findings contribute to the scientific discourse by shedding light on the potential benefits of the Kelly plication method in managing UI associated with pelvic organ prolapse. It is essential to acknowledge and consider these limitations in the context of the study's contributions to our understanding of UI management. Further research with extended follow-up periods and larger, more diverse subject populations may provide additional insights into the comparative effectiveness of various surgical interventions for UI.

CONCLUSION

Based on the findings of this study, it can be concluded that the Kelly plication method effectively reduces urinary incontinence (UI) symptoms in patients, leading to a significant improvement in the mean results of urinary pad tests and a higher reported quality of life among the subjects. The success rate of the Kelly method in improving the condition of UI in this study was 58.06%. This research focuses on the effectiveness of the Kelly plication method in patients who underwent concurrent prolapse surgery. It examines the substantial reduction in urinary incontinence symptoms and the concurrent improvement in the quality of life among these specific patient populations. The findings highlight the potential of the Kelly method as a viable treatment option for UI associated with pelvic organ prolapse, offering valuable insights to the field of urology with implications for clinical practice and patient care in this specific context.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 79–88

OPEN ACCESS

Original Article

The Correlation between Volatile Organic Compounds (VOC) with Leukotriene B4 and Eosinophil Counts in Chronic Obstructive Pulmonary Disease Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1035

Accepted: October 02nd, 2023
Approved: February 22th, 2024

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Publisher's Note:
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Abstract

Background : Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by increasing Leukotriene B4 (LTB4) and eosinophil counts. Volatile organic compounds (VOCs) have shown promise as non-invasive biomarkers, reflecting COPD pathophysiology. Identifying specific VOCs associated with increased LTB4 and eosinophil counts could lead to the discovery of potential biomarkers for COPD severity or progression. This study aims to investigate the correlation between VOCs and leukotriene B4 (LTB4) levels, as well as eosinophil counts counts in COPD patients.
Methods : Using an observational-analytic method with a case-control approach, 20 COPD patients and 20 controls were enrolled from the respiratory outpatient department of Dr. Saiful Anwar General Hospital, Malang. VOC levels were measured using a breath analyzer, while LTB4 levels were determined through enzyme-linked immunosorbent assays. Spearman's correlation tests examined associations between VOCs, LTB4, eosinophil counts, and comorbidity, with Mann-Whitney tests comparing results against the control group. Data significance was set at $p < 0.05$.
Results : There were 40 COPD patients and 40 controls in this study. There were significant differences between VOCs in the COPD group and the control group ($p < 0.05$). LTB4 level significantly increased in the COPD group than in the control group ($p < 0.001$), and there was no difference in the eosinophil level. There was a correlation between LTB4 and VOC level of C_2H_5OH in COPD patients ($p = 0.009$; $r = 0.410$). There was no correlation between eosinophil counts and VOCs ($p = 0.939$). The level of VOCs was significantly different between patients with only COPD and patients with COPD and comorbid lung cancer ($p < 0.05$).
Conclusion : There is a correlation between VOC and LTB4 in COPD patients.

Keywords : Volatile Organic Compounds, Leukotriene B4, Eosinophil, Chronic Obstructive Pulmonary Disease

INTRODUCTION

Chronic obstructive pulmonary disease, or known as COPD, is a disease characterized by persistent respiratory symptoms due to exposure to toxic gases or particles that cause airway or alveolar abnormalities.[1] COPD is caused by a complex interaction between genetics and the environment. The main risk factor for COPD is smoking, but other factors that can influence include age, gender, lung development, particulate matter exposure, socioeconomic status, asthma, hyperreactivity, chronic bronchitis, and infection.[2] The incidence of COPD is increasing every year. The results of the 2018 Basic Health Research (Riskesdas) show that the prevalence of COPD in Indonesia is 3.7% or around 9.2 million people.[3] According to the WHO, 2.9 million people die from COPD and it is estimated that by 2030, COPD will be the third most common cause of death in the world.[4]

The standard technique for diagnosing COPD is spirometry. However, spirometry can only show restrictions in the airway without identifying the cause of these restrictions.[5] VOC is a compound with a light molecular mass, a low boiling point, and relatively high vapor pressure; it also evaporates easily. VOC can come from endogenous or exogenous sources.[6] VOC is used as the newest modality to identify lung diseases. Analysis of the VOC can be used as a non-invasive, fast, and precise investigation to diagnose COPD.[7] There are several techniques often used to collect data and to detect and analyze VOC gases, often including gas chromatography (GC) and electronic nose (eNose) as the modalities, Mass spectrometry (GCMS) or flame ionization detection (GC-FID), proton transfer reaction mass spectrometry (PTR-MS), selective ion flow tube mass spectrometry (SIFT-MS), laser spectroscopy, colorimetric sensors with matrices and gold nanoparticles. Sensors (VNP).[8]

COPD is a disease associated with inflammation and oxidative stress. According to research, levels of LTB4 and other inflammatory markers in the body such as IL-8 will increase in COPD preogression.[9] LTB4 functions as a neutrophil and T-cell chemoattractant, which has a correlation with lung function progression.[10] In some COPD patients, eosinophils contribute to airway obstruction biomarker. One-third of stable COPD patients are known to have elevated eosinophil counts. This can determine which patients will benefit from inhaled corticosteroids and determine the prognosis of patient exacerbations.[11] Identifying specific VOCs associated with increased LTB4 and eosinophil counts could lead to the discovery of potential biomarkers for COPD severity or progression. Based on existing problems, theories, and supporting journals, the researchers were interested in analyzing VOC in COPD patients and its relationship with LTB4 and blood eosinophil levels.

METHODS

This study used an observational-analytic method with a case-control design approach to assess differences in VOC, LTB4 levels, and blood eosinophils in stable COPD patients at Dr. Saiful Anwar General Hospital, Malang. This study was conducted in AugustSeptember 2022 at the outpatient clinic of Dr. Saiful Anwar General Hospital, Malang. This research has an ethical aprroval with No 400/14/K.3/102.7/2023 from Health Research Ethics Commission of General Hospital Dr. Saiful Anwar.

The population of this study is stable COPD patients who visit the pulmonary polyclinic at Dr. Saiful Anwar General Hospital, Malang, as subjects and PPDS Pulmonology and Respiratory Medicine Specialist Medical Education Program, Faculty of Medicine, University of Brawijaya, as control subjects.

This research applies strict inclusion and exclusion criteria to ensure sample homogeneity and the validity of research outcomes. Inclusion criteria involve patients with stable COPD or those who have undergone treatment post-acute exacerbation and are currently in a stable condition. The research subjects range in age from 40 to 70 years and express willingness to participate after receiving adequate explanations and signing informed consent. On the other hand, there are exclusion criteria that encompass subjects experiencing acute COPD exacerbation symptoms, such as increased shortness of breath, heightened cough frequency, increased sputum production, and changes in sputum color. This is done to ensure that research subjects are in a stable condition and not influenced by ongoing exacerbation episodes. Furthermore, the samples were divided into two research groups, namely research subjects and controls. Data on serum levels of VOC, leukotriene B4, and eosinophil were collected from each group.

The data obtained were to be recorded on the research sheet and were then processed and analyzed. Data analysis method used in this study include the Chi-square test or Fisher's exact test for categorical data. Mann-Whitney test or independent t-test were used for the analysis of variables between the two groups. Meanwhile, the correlation between variables was analyzed using Pearson's or Spearman's correlation test with significant level of $p<0.05$. The statistical testing tool used to analyze the data is SPSS version 26.

RESULTS

The research subjects consisted of 80 subjects making the 2 research groups. The research group consisted of 40 healthy control subjects (pulmonary PPDS) and 40 subjects in the COPD case group. The sociodemographic characteristics of the research subjects can be seen in Table 1. Normality test used Shapiro-Wilk test. In this study, it is shown that age, height, platelet

TABLE 1
Sociodemographic Characteristics of the Research Subjects

Characteristics		Healthy control (n= 40)	COPD cases (n= 40)
Gender	Man	22 (55%)	33 (82.5%)
	Woman	18 (45%)	7 (17.5%)
Age	year	31.35 (± 3)	64.73 (±10.6)
Height	cm	164.9 (± 9.0)	162.1 (±4.8)
Weight	kg	70.15 (± 15.9)	52.4 (±8.7)
Body Mass Index (BMI)	kg/m^2	25.6 (± 4.2)	19.9 (±2.9)
Smoking Status	Do not smoke	36 (90%)	0 (0%)
	Former smoker	0	4 (10%)
	Passive smoker	2 (5%)	10 (25%)
	Active smoker	2 (5%)	26 (65%)
Complaint	Hard to breathe	0	27 (67.5%)
	Cough	0	23 (57.5%)
	Sputum production	0	11 (27.5%)
	Chest pain	0	2 (5%)
Comorbidities	Lung cancer	0	20 (50%)
	Pulmonary TB	0	2 (5%)
	Asthma	6 (15%)	0

count, and compound C6H6 had a normal distribution so the process was continued with an independent t-test analysis. Normality analysis of body weight, Hb levels, leukocytes, hematocrit, eosinophils, LTB4 levels, FEV1/FVC values, FEV1, compounds O_2, CO_2, O_3, CO_2, C_2H_5OH, CH_2O, C_7H_8, C_3H_6O, NH_4, C_6H_{14}, NO_2, CO, NH_3, CH_4, and C_3H_8 had an abnormal distribution, so a Mann-Whitney analysis was performed.

Laboratory Examination Results and Spirometry

This study showed that there were significant differences in LTB4 levels, Hb levels, hematocrit values, lymphocyte values, and spirometry results between controls and COPD patients. LTB4 levels were higher in COPD patients compared to the controls ($p = 0.020$; $p = 0.000$; $p = 0.000$, $p = 0.000$, $p = 0.000$ ($p < 0.05$)) (Table 2).

Examination Results of Levels of Volatile Organic Compounds

There were significant differences in the parameters CO_2, C_2H_5OH, C_3H_6O, NO_2, CO, NH_3, C_6H_6, and C_3H_8 between the case group and the control group. The mean of CO_2, C_3H_6O, and NO_2 were significantly lower in the case group than in the control group (2,849.58 vs 1,577.75; 11.1 vs 4.8; and 0.82 vs 0.06, respectively). Meanwhile, the mean of C_2H_5OH, CO, NH_3, and C_3H_8 were significantly higher in the case group than in the control group (1.85 vs 1.4, 0.6 vs 0.025, 0.004 vs 0.0001 and 3.2 vs. 2.34) respectively. There is no significant difference in the mean parameters CH_2O and C_7H_8 between the two groups (Table 3).

Relationship between Serum LTB4 and Serum Eosinophil and Spirometry Parameters

Statistical test results demonstrated a relationship between serum LTB4 levels and serum neutrophils and FEV1. No significant relationship was found between LTB4 and eosinophil counts. The FEV1 parameter was found to have no relationship with serum LTB4 (Table 4).

The Relationship between FEV1 and VOCs

The results of the statistical tests revealed that the CO_2 parameter has a significant relationship with FEV1 ($p = 0.049$), which was then tested using the Spearman's method with a correlation result of -0.313. The parameter C_2H_5OH shows a significant relationship with FEV1. Spearman's test showed a moderate correlation between FEV1 and C_2H_5OH (correlation coefficient of 0.410).

TABLE 2
Laboratory Data and Spirometry

Characteristics		Control	COPD	*p-values*
LTB4		84.04 ± 89.79	244.1 ± 186.9	<0.001[b]
Laboratory	Hb	14.26 ± 1.96	12.23 ± 2.17	0.000[b]
	Leukocytes	7,595.75 ± 1,876.91	9,981.25 ± 3,800.29	0.002[b]
	Hematocrit	43.65 ± 4.50	37.24 ± 6.54	0.000[b]
	Platelets	331,950.0 ± 68,313.36	318,425.0 ± 121,215.61	0.540[a]
	Eosinophils (%)	1.98 ± 1.45	2.01 ± 1.98	0.939[b]
	Eosinophils (cells)	136.5 ± 95.58	216.87 ± 230.92	0.623[b]
	Lymphocytes	27.81 ± 7.26	18.37 ± 10.11	0.000[a]
Spirometry	FEV1/FVC	122.89 ± 147.93	62.06 ± 8.08	<0.001[b]
	FEV1	89.47 ± 9.29	46.07 ± 9.89	<0.001[b]

[a]Independent t-test; [b]Mann-Whitney test

TABLE 3
Comparison of VOC Compounds in Research Subjects

VOC compounds	Control	COPD	*p-values*
CO_2	2,849.575 ± 0.324	1577,75±,1052,701	< 0.001[b]
C_2H_5OH	1.376 ± 0.324	1,855±,701	< 0.001[b]
CH_2O	0.0763 ± 0.02	0.075±.021	0.776[b]
C_7H_8	0.005 ± 0.002	0.005±.002	0.776[b]
C_3H_6O	11.115 ± 3.543	4,814±2,378	< 0.001[b]
NH_4	1.414 ± 1.457	0.594±1.035	0.776[b]
C_6H_{14}	0.35 ± 0.046	0.286±.093	0.776[b]
NO_2	0.816 ± 0.390	0.055±.148	< 0.001[b]
CO	0.025 ± 0.042	0.603±.243	< 0.001[b]
NH_3	0.0001 ± 0.00	0.004±.012	0.022[b]
CH_4	0.080 ± 0.020	0.189±.230	0.310[b]
C_6H_6	0.602 ± 0.019	0.634±.048	< 0.001[a]
C_3H_8	2.343 ± 0.619	3.195±1.253	0.001[b]

[a]Independent t-test; [b]Mann-Whitney grades

Meanwhile, the C_3H_6O and NO_2 parameters show a negative correlation with FEV1, with correlation coefficients of -0.417 and -0.316, respectively. On the other hand, the parameters CO, NH_3, C_6H_6, and C_3H_8 do not show a significant relationship with FEV1, so the Spearman's correlation test does not give significant results. (Table 5).

Relationship Between LTB4 and Serum Neutrophil Levels with VOC Levels

There is a relationship between serum LTB4 and VOC parameters. Of the 8 VOCs tested, only 1 parameter has a significant relationship with LTB4, namely C_2H_5OH ($p = 0.009$). Then, the test was continued with Spearman's test, which produced a correlation coefficient of 0.410, meaning that there is moderate strength between the two

TABLE 4
The relationship between serum LTB4 levels and eosinophil counts and spirometry parameters (FEV1)

Relationship between variables			Correlation coefficient	*p-value*
Serum LTB4	with	Eosinophil %	-0.179	0.112
	with	Absolute Eosinophils	-0.103	0.364
	with	FEV1	-0.173	0.125

*Paired t-test, p=0.05

TABLE 5
The relationship between FEV1 values and VOC levels

Relationship between variables			Correlation coefficient	*p-value*
FEV1	with	CO_2	-0.313	0.049
	with	C_2H_5OH	0.410	**0.009**
	with	C_3H_6O	-0.417	0.007
	with	NO_2	-0.316	0.047
	with	CO	0.166	0.305
	with	NH_3	0.130	0.423
	with	C_6H_6	0.294	0.066
	with	C_3H_8	-0.025	0.876

parameters. On the other hand, the remaining 7 VOC parameters have a statistically non-significant relationship with serum LTB4 (Table 6).

Relationship Between Serum Eosinophil Levels and VOC Levels

Statistical test results showed that none of the 8 VOC parameters have a significant relationship with eosinophil counts. The p-values of each VOC parameter are as follows: CO_2 (0.593), C_2H_5OH (0.295), C_3H_6O (0.933), NO_2 (0.954), CO (0.283), NH_3 (0.870), C_6H_6 (0.163), and C_3H_8 (0.990). This means that serum eosinophil levels are not related to VOC parameters (Table 7).

DISCUSSION

In this study, the age of patients with COPD is older than the age of those in the control group. COPD is 23 times more common in older people, and being in the elderly population is a significant risk factor for COPD. Aging is the progressive degeneration of tissues that affects the structure and function of vital organs. Age-related diseases arise when physiological anti-inflammatory and antioxidant mechanisms fail to protect the body from damage caused by chronic inflammation and increased reactive oxygen species (ROS). This imbalance leads to cellular and/or tissue damage that, combined with common COPD risk factors such as smoking, contributes to the development of COPD in older adults. From the third decade of life, age-related decline in lung function and structural dysfunction begins. Loss of function in the elderly may contribute to the "senile lung" phenomenon, which is characterized by alveolar enlargement in the absence of wall damage. As lung function declines and age-related structural changes occur, the lung's defense mechanisms become less effective. This increases the risk of lung infections and leads to decreased protective responses against oxidative stress and inflammation.[12]

Smoking may be an early trigger of proteostatic dysregulation in COPD. Oxidative stress caused by cigarette smoking causes protein breakdown and leads to the accumulation of misfolded proteins in the endoplasmic reticulum (ER), leading to the ER stress response. The unfolded protein response (UPR) is a compensatory cellular response to ER stress. This process attempts to restore homeostasis by reducing protein synthesis and increasing the degradation of misfolded proteins via the ubiquitin-proteasome pathway. If the UPR is unable to handle stress, the process of apoptosis occurs. In addition to protein degradation, cigarette smoking reduces proteasomal activity in alveolar epithelial cells, resulting in poor clearance of damaged proteins. Long-term accumulation of inactive proteins eventually leads to apoptosis and triggers chronic

TABLE 6
Relationship between serum LTB4 levels and VOC levels

Relationship between variables			Correlation coefficient	*p-value*
Serum LTB4	with	CO_2	0.229	0.155
	with	C_2H_5OH	0.410	**0.009**
	with	C_3H_6O	-0.180	0.268
	with	NO_2	-0.203	0.209
	with	CO	-0.151	0.353
	with	NH_3	-0.195	0.227
	with	C_6H_6	-0.273	0.089
	with	C_3H_8	0.239	0.137

TABLE 7
The relationship between serum eosinophil levels and VOC levels (Spearman's test)

Relationship between variables			Correlation coefficient	*p-value*
Eosinophil counts	with	CO_2	-0.061	0.593
	with	C_2H_5OH	0.119	0.295
	with	C_3H_6O	-0.010	0.933
	with	NO_2	0.006	0.954
	with	CO	-0.122	0.283
	with	NH_3	-0.019	0.870
	with	C_6H_6	-0.157	0.163
	with	C_3H_8	-0.001	0.990

inflammation, thereby contributing to the pathogenesis of COPD.[13] In this study, the majority of COPD patients were male. The results of this study are consistent with previous studies, which show that men make up 64% of patients with COPD.[14]

The Comparison of Laboratory Results and VOC between COPD and Controls

This study showed that there is an increase in LTB4 levels in COPD patients compared to the controls. In COPD patients, cytokine levels increase as macrophages and alveolar epithelial cells release LTB4, a chemical factor that attracts immune cells. Macrophages and alveolar cells also produce IL-8/CXCL8 and growth-related oncogene (GROα)/CXCL1, which increase the inflammatory response by recruiting more leukocytes from the blood to the site of inflammation. Other chemotactic factors such as CXCL5 and CXCL8 can also increase the migration of neutrophil cells in COPD patients.[15] Leukotriene B4 (LTB4) is a chemokine that influences the accumulation of granulocytes and macrophages at sites of inflammation. BLT1 is a highly specific receptor for LTB4 that is expressed on the surface of inflammatory and immune cells. Currently, inhibition of the LTB4/BLT1 pathway using BLT1 antagonists is used to reduce mitochondrial dysfunction in various inflammatory diseases as well as sepsis, asthma and arthritis.[16]

This study also shows that the leukocyte count of COPD patients increased when compared to the controls. Macrophages, essential for lung homeostasis and defense against inhaled threats, increase substantially in COPD lungs. However, half of COPD patients, despite elevated macrophages, show chronic bacterial colonization, indicating innate immune dysfunction. These macrophages originate from circulating monocytes recruited to the lungs, undergoing further differentiation in the tissue.[17] This study showed that the lymphocytes of COPD patients were significantly lower than those of the controls. Persistent inflammation is key in COPD

development, with lymphocytes crucial in its progression. Fibrotic conditions reveal infiltration of macrophages and T lymphocytes. Severe COPD cases, as seen in bronchoalveolar lavage tests, exhibit a notable rise in macrophages and neutrophils but a decrease in lymphocytes. Lymphopenia may signal a weakened immune system, heightening infection risk and potentially indicating a systemic response to stress.[18]

This study shows that patients with COPD experience a significant decrease in lung function compared to controls. COPD results in decreased lung function due to various factors, including oxidative stress, airway inflammation, cellular aging, and cell death induced by cigarette smoke. Cigarette smoke-generated excessive reactive oxygen species (ROS) damages the lungs, contributing to COPD pathogenesis. Smokers exhibit reduced Nrf2 levels, a key protector against oxidative stress, resulting in insufficient antioxidant production. Oxidative processes not only impact lung damage but also induce cellular senescence in epithelial and stem cells. Lung aging leads to the development of senescence-associated secretory phenotypes (SASPs), releasing inflammatory molecules and causing chronic damage to lung structures.[19] The results of this research are consistent with previous studies, which showed that patients with asthma and COPD show a decrease in FEV1, FVC, and peak expiratory flow rate compared to normal people.[20] In this study, several VOC compounds are found to be significantly different in COPD patients. VOCs that can be identified from cellular and enzymatic metabolic pathways, on the other hand, can be used to better understand the underlying complex biological processes so that they can become new therapeutic targets. Labeled VOC compounds can be used to identify specific cellular or microbial activity in respiratory tract diseases.[21]

This study shows that there are 8 compounds that have significantly different potential as markers in COPD. These compounds and their metabolites hinder alveolar macrophages (AM), causing increased airway leakage, harmful ROS generation, and disruption of the lung's antioxidant/oxidant balance. Ethanol exposure impairs pathogen clearance through reduced CBF, impaired alveolar macrophage function, and affects the adaptive immune system. This compromised CBF and weakened immune response contribute to infectious lung diseases, like bacterial pneumonia in alcoholics. Ethanol's effects on epithelial permeability and fluid clearance, through ion channel dysregulation and increased TGF-β, also contribute to lung fibrosis.[22]

This study shows that there is an increase in C3H6O or acetone compounds. Patients with COPD are older on average and tend to lose skeletal muscle mass as the disease progresses. A study by Shahzad *et al*. showed that the average exhaled acetone level of healthy patients (0.66 ppm) was higher than those with COPD (0.50 ppm). Blood plasma of COPD patients shows low concentrations of amino acids, abnormalities in glycometabolism, decreased metabolites related to immune functionincluding glutamineand increased metabolism of fats including acetoacetic acid and acetone, which are products of fatty acid catabolism.[23] Research by Van Berkel (2010) aims to evaluate the VOC profile that differentiates COPD patients from controls.[24]

Based on research by Basanta *et al*. (2012) indicates that the use of VOCs could differentiate patients with COPD from controls. The results of this study indicate that there are 11 aldehyde compounds that can be used to differentiate COPD patients from controls. However, the metabolism of this aldehyde is increased in smoking patients and can be reduced when N-acetylcysteine is administered.[5] Other studies have also stated that ketone compounds are increased in AECOPD patients compared to COPD patients. In addition, some of these VOCs are also associated with the presence of potential bacterial pathogens.[7]

The difference in exhaled benzene (C_6H_6) levels in the case group and the controls in this study is significant. A study by Filipiak *et al*. (2012) found that certain VOCs were detected significantly more frequently in the exhaled breath of smokers compared to nonsmokers ($p<0.05$), namely benzene, toluene, and hexane with specificities above 90%.[25] Propane (C_3H_8) differed significantly between the case and control groups. Propane belongs to the class of VOC pollutants commonly used in cooking, heating, and grilling foods. In addition, propane is one of the aldehydes that is a constituent of cigarette smoke.[25] There were marked increased levels of carbon monoxide (CO) in the case group compared to controls. In non-smokers, exhaled CO is increased due to endogenous production and in a condition of pulmonary inflammation. A study in India in 2018 showed that, in COPD, exhaled CO levels increased > 3 times more than in healthy individuals.[26] A significant difference in elevated carbon monoxide (CO) levels was found between the disease group and the control group. A study in India in 2018 showed that COPD levels in the exhaled air of COPD patients increased more than 3 times compared to healthy individuals.[26]

Nitrogen dioxide (NO_2) levels were higher in the control group than in the study group. Sources of NO_2 are cigarette smoke, and combustion devices such as ovens, stoves, and water heaters. Studies show exposure to NO_2 can increase the risk of exacerbation of asthma and COPD patients. In addition, NO_2 is an ambient air pollutant, which is an irritant to the airways.[2] Ammonia (NH_3) is a product of the hydrolysis of urea, which is involved in the nitrogen cycle. In exhaled air, NH_3 showed no difference between normal subjects and patients with cystic fibrosis, but it increased in patients with asthma and ARI. Increased urea levels are in line with increased oxidative stress. Brushing teeth and rinsing can reduce NH_3 levels

in exhaled air. Another research by Shahzad *et al*. in 2022 showed NH_3 in exhaled air can be a useful biomarker in COPD because it has a positive relationship with FEV1 values.[28]

Relationship between FEV1 and VOCs

There are four VOC parameters that showed a significant relationship with FEV1 values, namely CO_2, C_3H_6O, NO_2, and C_2H_5OH. There is a negative correlation between the CO_2 parameter and the FEV1 value. CO_2 retention can be used as an indicator of the severity of obstruction in COPD patients. This retention is associated with decreased ventilation function, respiratory muscle weakness, worsening of respiratory symptoms, lung damage, and respiratory failure. The study conducted by Wei *et al*. showed that CO_2 retention was associated with worse FEV1 values in acute exacerbation of COPD.[29] The negative correlation results of this study may be due to the stable condition of COPD patients with the use of bronchodilators thereby demonstrating better CO_2 exhalation.

In this study, it was found that there is a negative correlation between FEV1 values with C_3H_6O and NO_2; that is, the lower the FEV1 value, the higher the levels of C_3H_6O and NO_2 in the exhaled air. A study also indicated that C_3H_6O levels in exhaled air were higher in smokers with lung cancer compared to healthy active smokers. A positive correlation was found between FEV1 and C_2H_5OH. Shahzad *et al*. in their study showed that the ethanol (C_2H_5OH) levels of COPD patients were almost the same as those of healthy patients (0.96 ppm vs 1.09 ppm). In addition, exhaled ethanol levels measured based on the degree of COPD obstruction were also relatively the same (mild: 0.92 ppm; moderate: 1.07 ppm; severe: 0.93 ppm).[28]

The Relationship between LTB4 and Eosinophils with VOC

The research findings indicated that there is a correlation between serum LTB4 and ethanol, from the eight VOC parameters tested. An increase in serum LTB4 will cause an increase in ethanol levels in exhaled air. Research by Allers *et al*. showed higher levels of ethanol in exhaled air in smokers compared to non-smokers; although, this difference was not significant in the COPD group when compared to the healthy group.[30] None of the VOC parameters showed a significant association with eosinophil counts. Until now, no study has analyzed the correlation between LTB4 and eosinophil counts with VOC parameters in COPD cases. In theory, oxidative stress in the airways and lungs can result in the accumulation of inflammatory cells, including macrophages and neutrophils, which increase ROS production. LTB4 is produced from the metabolism of arachidonic acid in lipid membranes in response to increased ROS. LTB4 acts as a chemoattractant for neutrophils, which plays an significant role in airway inflammation in COPD patients and contributes to lung tissue damage. Meanwhile, the increased VOC of expired air in COPD cases is a product of lipid peroxidation in lipid membranes that is not related to arachidonic acid metabolism, which plays an significant role in the airway inflammation process in COPD patients and contributes to lung tissue damage. Meanwhile, the increased VOC of expired air in COPD cases is a product of lipid peroxidation in lipid membranes that is not related to arachidonic acid metabolism.[4]

Role of Eosinophils in COPD and VOC

This research has revealed that there are no distinctions in eosinophil levels between the COPD group and the control group. Furthermore, eosinophils do not appear to be associated with all types of volatile organic compounds (VOCs). Eosinophils play a role in the inflammatory response seen in COPD. In specific situations, inflammation attracts eosinophils to the lungs, where they release various chemicals, including chemokines (such as CCL5, CCL11, CCL13), cytokines (such as interleukin (IL)-2, IL-3, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-25), and cytotoxic granular substances (such as major basic proteins, eosinophil cationic proteins, eosinophil peroxidases, eosinophil-derived neurotoxins), all contributing to the inflammatory process. In a state of equilibrium, eosinophils circulate in the bloodstream and adhere to the bronchial vascular endothelium when necessary. Eosinophil infiltration into the airways occurs only when inflammatory signals induce the expression and/or activation of specific adhesion molecules on the endothelium and bronchial vascular epithelium. This recruitment to the airway is regulated by chemokines like CCL5, 7, 11, 13, 15, 24, and 26, along with their corresponding receptors, such as CCR1, CCR2, and CCR3. This interaction between chemokines and receptors, in conjunction with chemoattractant receptor homologous molecules found on type 2 helper T cells and their ligand, prostaglandin D2, plays a crucial role in this process.[31]

In a study conducted by Nishimura *et al*. (2012), it was demonstrated that a rapid decline in lung function is indicative of more severe emphysema and lower levels of circulating eosinophils. This indirectly suggests a possible connection between emphysema and blood eosinophil counts in COPD.[32] Another study by Papaioannou *et al*. (2017), involving 98 COPD patients, reported that individuals with significant emphysema, affecting ≥15% of lung parenchyma, had lower blood eosinophil counts compared to those without emphysema.[33] These findings are consistent with our observations of longer survival in COPD patients with higher eosinophil counts.

This study also highlights the presence of several VOCs that significantly differ between COPD patients

and healthy controls. Additionally, certain VOCs can differentiate between COPD patients with and without comorbidities. However, it's important to note that this study has limitations, including the consideration of pollutant exposure locations and the absence of analysis regarding other comorbidities such as diabetes, hypertension, and oral diseases. These various factors are believed to influence the VOC profiles of COPD patients.

CONCLUSION

Based on the results and discussion above, it can be concluded that there are differences in the profile of volatile organic compounds (VOC) and levels of leukotriene B4 in COPD patients and the control group. There is no difference in eosinophil counts in COPD patients and the control group. There is a relationship between serum leukotriene B4 and VOC for the C2H5OH component in COPD patients. There is no relationship between differences in volatile organic compound (VOC) profiles and eosinophil serum levels in COPD patients and control patients. The researchers suggest that it is necessary to check the VOC levels in ambient air to prove whether or not there is an environmental effect on the research results and to take homogeneous samples between COPD case groups and healthy controls.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 89–93

OPEN ACCESS

Original Article

The Effectiveness of E-Backnshou Exercise to The Improvement of Neck, Shoulder and Back Pain in Computer Vision Syndrome Patient

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1017

Accepted: August 14th, 2023
Approved: March 1st, 2024

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Abstract

Background : Extra-ocular complaints of Computer Vision Syndrome (CVS) are neck, shoulder, back pain. The 20-20-20 rule and E-BACKNSHOU exercise are expected to improve accommodative mechanisms, ocular surface of the eye and extra ocular symptoms of CVS. This study was aimed to proving the effectiveness of E-BACKNSHOU exercise for the improvement of neck, shoulder and back pain in CVS patient.
Methods : The research design was Pre-Post Test with Control Design. Subjects were 30 medical students of Faculty of Medicine, Diponegoro University, Semarang, Indonesia who experienced CVS and neck, shoulder and back pain. The treatment group got the 20-20-20 rule and E-BACKNSHOU exercise and the control group got the 20-20-20 rule for 1 month. Pain was measured by Visual Analogue Scale (VAS). Statistical test was conducted using paired t-test, unpaired t-test and Chi-Square. Value of significance $p<0.05$.
Results : There were significant differences in VAS score of neck, shoulder, upper back pain (p=0.00), and low back pain (p=0.022) before and after the intervention in the treatment group and VAS score of neck (p=0.002), shoulder (p=0.020), upper back (p=0.011), and low back pain (p=0.019) in the control group. Delta VAS score of the treatment group was greater than the control group and there was a significant difference in delta VAS score of shoulder pain (p=0.030), but there were no significant differences in delta VAS score of neck (p=0.934), upper back (p=0.356), and low back pain (p=0.150).
Conclusion : The effectiveness of 20-20-20 rule and E-BACKNSHOU exercise is better than the 20-20-20 rule alone on treating neck, shoulder and back pain in CVS patient.

Keywords : CVS, E-BACKNSHOU exercise, pain

INTRODUCTION

Excessive use of computers can cause Computer Vision Syndrome, neck, shoulder and back pain. Computer Vision Syndrome (CVS) which is also referred as digital eye strain, is defined as a collection of problems related to eyes and vision caused by prolonged use of computers, tablets, e-readers, cellular phones or cellphones.[1] Symptoms of CVS are broadly classified into four categories: 1) asthenopic (sore eyes, eye strain), 2) ocular surface related (dry eye, irritation, watering), 3) visual (double vision, blurred vision, slowness of focus change), 4) extra ocular (shoulder pain, neck pain, back ache).[2]

E-BACKNSHOU exercise is a range of motion and stretching (flexibility) exercise therapy for the eyes, extremities, back, neck, and shoulders with Central Java musical accompaniments created by the researchers. The 20-20-20 rule consists of every 20 minutes, the subjects shift their eyes to look at an object at least 20 feet away, for at least 20 seconds.

Therefore, in this study, the researchers want to prove that the improvement of neck, shoulder, upper and low back pain in CVS patient is better by the addition of E-BACKNSHOU exercises rather than the 20-20-20 standard therapy method only.

METHODS

This research is an experimental research, pre-post test with control group design and was conducted at Faculty of Medicine, Diponegoro University at Semarang from May to June 2019.

Based on the calculation, the sample size needed for this study were 15 subjects in the treatment group and 15 subjects in the control group with a total of 30 subjects. The method of selecting samples was simple random sampling. The research subjects were students of the Faculty of Medicine, Diponegoro University, Semarang who met the criteria, which are those who experienced CVS, neck pain, shoulder pain and back pain after a minimum of 4 hours using computer or cellphone without rest, or resting time less than 10 minutes after using computer. Diagnosis of CVS was total score of more than 6 point in Computer Vision Syndrome Questionnaire (CVS-Q). The exclusion criteria were subjects who had a history of mental disorders, high myopia, and refused to participate. This study has been approved by Diponegoro University Ethical Review Board with number 121/EC/KEPK/FK-UNDIP/V/2019.

The treatment group got the 20-20-20 rule and E-BACKNSHOU exercises, while the control group only got the 20-20-20 rule. The 20-20-20 rule consists of every 20 minutes, the subjects shift their eyes to look at an object at least 20 feet away, for at least 20 seconds. E-BACKNSHOU exercises were range of motion and stretching exercises for extremity, eye, back, neck, and shoulder with 18 minutes and 48 seconds duration, with warming up for 1 minute 36 seconds repeated once (moving eyes to all 8 directions, range of motion exercise of the neck by moving the head to all directions, range of motion of both shoulder and elbow), main exercise 15 minutes 36 seconds repeated 3 times each (elbow, wrist and finger stretching, lower extremity stretching, moving eyes to all 8 directions, blink for 20 seconds, neck and back stretching) and cool down 1 minute and 36 seconds repeated once (moving eyes to all 8 directions, neck and arm stretching), 3–5 times a week for 4 weeks.

Hypothetical testing for differences in VAS score of neck, shoulder pain, upper and low back pain improvement before and after the intervention in each group were done using paired t-test. Hypothetical testing for differences in VAS score of neck, shoulder, upper back pain and low back pain after the intervention between both groups were done using unpaired t-test. Hypothetical testing for differences in score improvement between the delta treatment group and the control group was done using unpaired t-test. Hypothetical testing for VAS scores improvement on neck pain, shoulder pain upper back pain and low back pain events after the interventions between the treatment and control groups were done using Mann-Whitney U test. P value is considered significant if <0.05. Statistical analysis was performed using SPSS version 21 for Windows.

RESULTS

There were significant differences in VAS score of neck pain (p=0,000), shoulder pain (p=0.000), upper back pain (p=0.000), and low back pain (p=0.022) before and after the intervention in the treatment group. There were significant differences in VAS score of neck pain (p=0,002), shoulder pain (p=0.020), upper back pain (p=0.011) and low back pain (p=0.019), before and after intervention in the control group. The VAS score of neck pain, shoulder pain, upper back pain and low back pain before and after intervention in the treatment and control group (Table 1).

The VAS scores of neck, shoulder, upper back pain after the intervention in the treatment group were lower than in the control group, but there were no significant differences VAS scores of neck (p=0.808), shoulder (p=0.600), upper back pain (p=0.725) after the intervention between treatment and control group. There were significant difference in VAS score low back pain after the intervention (p=0.013) between the treatment group and the control group (Table 2).

Delta VAS score of treatment group were greater than the control group, but there were no significant differences in delta VAS score of neck pain (p=0.934), upper back pain (p=0.356), and low back pain (p=0.150)

TABLE 1
VAS score neck, shoulder, upper and low back pain, before and after intervention in each group

	Treatment Group			Control Group		
	Mean (SD) before intervention	Mean (SD) after intervention	*p*	Mean (SD) before intervention	Mean (SD) after intervention	*p*
VAS score neck pain	4.80 ± 1.373	2.13 ± 1.995	0.000	4.93 ± 1.486	2.33 ± 2.440	0.002
VAS score shoulder pain	5.00 ± 1.254	2.13 ± 1.807	0.000	3.80 ± 2.145	2.53 ± 2.295	0.020
VAS score upper back pain	4.20 ± 1.568	1.93 ± 1.792	0.000	3.80 ± 2.541	2.20 ± 2.305	0.011
VAS score low back pain	4.13 ± 1.727	2.73 ± 1.944	0.022	2.87 ± 2.356	1.07 ± 1.438	0.019

TABLE 2
VAS score neck, shoulder, upper and lower back pain after intervention between groups

	Treatment Group Mean (SD)	Control Group Mean (SD)	*p*
VAS score neck pain	2.13 ± 1.995	2.33 ± 2.440	0.808
VAS score shoulder pain	2.13 ± 1.807	2.53 ± 2.295	0.600
VAS score upper back pain	1.93 ± 1.792	2.20 ± 2.305	0.725
VAS score low back pain	2.73 ± 1.944	1.07 ± 1.438	0.013*

between the treatment group and the control group. There were a significant difference in delta VAS score of shoulder pain (p=0.030) between the treatment group and the control group. The delta VAS scores of neck pain, shoulder pain, upper back pain and low back pain between group can be seen in Table 3.

The results showed that there were no significant differences in the symptoms of neck pain (p=0.705), shoulder pain (p=0.690), upper back pain (p=0.099), low back pain (p=0.256) after the intervention between group (Table 4).

DISCUSSION

Computer Vision Syndrome is caused by continuous accommodation involving the intra and extra ocular muscles so that the eye muscles experience fatigue,[3–7] causing static positions in the neck muscles, shoulders, upper back and lower back. The static position causes the muscles to spasm and cause pain in the muscles.[3–7,8]

The treatment group got the 20-20-20 rule and E-BACKNSHOU exercises. The 20-20-20 rule aims to accommodate the eye so that the intra and extra ocular muscles can relax and blink 20 times to wet the surface of the eyeball. E-BACKNSHOU exercises consist of extra ocular muscles exercises (medial rectus, superior rectus, inferior rectus, lateral rectus, superior oblique, and inferior oblique), range of motion and stretching exercises in the muscles of the extremities, neck, shoulder and back. E-BACKNSHOU exercises, like other stretching exercises have been able to increase the range of joint motion, flexibility, stretch muscles, decrease muscle spasm, increase endorphin hormone production and decrease cortisol response.[9]

Previous study by Kurunhikattil (2016) stated that eye and neck exercises are very effective in reducing eye strain and neck pain. The eye exercise in this previous study was moving eyes toward right, left, up and down to relax the eye muscles. Neck exercise consists of moving neck right, left, up and down, rotating clockwise and counter-clockwise every 3 hours. E-BACKNSHOU eye exercises in this study used more direction of eye movement, compared to Kurunhikattil's study.[10]

Another study by Gaikwad (2021) stated that 4 weeks of isometric neck setting exercises and eye exercises, significantly improved pain on VAS and improving score of quality of life, compared to isometric neck exercises alone in subjects with bifocal lens.[11] 20-20-20 rule has induced significant changes in reducing CVS sign, although can't eliminate CVS completely, according to the previous study.[12]

E-BACKNSHOU exercises in this study used neck, shoulder, elbow range of motion, followed by stretching movements for eye, neck, shoulder, back and extremities.

TABLE 3
Delta VAS score neck, shoulder, upper and lower back pain between the treatment group and the control group

Delta	Treatment Group Mean (SD)	Control Group Mean (SD)	*p*
VAS score neck pain	2.67 ± 1.839	2.73 ± 2.463	0.934
VAS score shoulder pain	3.00 ± 1.852	1.53 ± 1.642	0.030*
VAS score upper back pain	2.53 ± 1.356	2.00 ± 1.732	0.356
VAS score low back pain	1.13 ± 1.598	2.20 ± 2.274	0.150

TABLE 4
Symptoms of neck pain, shoulder pain, upper back pain, low back pain after the intervention between group

Incidence	Treatment Group Mean (SD)	Control Group Mean (SD)	Total	*p value*
Neck pain (-)	6	5	11	0.705
Neck pain (+)	9	10	19	
Total	15	15	30	
Shoulder pain (-)	5	4	9	0.690
Shoulder pain (+)	10	11	21	
Total	15	15	30	
Upper back pain (-)	6	2	8	0.099
Upper back pain (+)	9	13	22	
Total	15	15	30	
Lower back pain (-)	4	7	11	0.256
Lower back pain (+)	11	8	19	
Total	15	15	30	

Compared to the previous studies, this study combined E-BACKNSHOU exercises with the 20-20-20 rule to decrease extraocular pain due to CVS. E-BACKNSHOU exercises has been able to improve the mechanism of extra ocular pathogenesis, namely musculoskeletal pain disorders including low back pain and shoulder pain.

The results showed significant differences in VAS scores of neck pain, shoulder pain, upper back pain, and lower back pain before and after the intervention in both the treatment and control groups. The difference is in the form of a decrease in the mean VAS score before and after the intervention in both the treatment and control groups. The decrease in CVS score were greater in the treatment group than in the control group. This shows that E-BACKNSHOU and the 20-20-20 rule both were effective in reducing the complaints of neck, shoulder, upper back pain and lower back pain.

VAS score of neck, shoulder, upper back pain after the intervention in the treatment group was lower than the control group, but there was no significant difference in VAS scores of neck, shoulder, upper, and lower back pain after the intervention between the treatment group and the control group. There was significant difference in VAS score of lower back pain after the intervention between the treatment group and the control group.

Delta VAS score of the treatment group was greater than control group, but there were no significant differences in delta VAS score of neck pain, upper back, and lower back pain between the treatment group and the control group. There was significant difference in delta VAS score of shoulder pain between the treatment group and the control group. This could be due to neck ROM and stretching component of E-BACKNSHOU in the intervention group that relaxed the shoulder muscles and

reducing pain.

The results showed no significant differences in the occurrence of neck pain, shoulder pain, upper back pain, and lower back pain after the intervention between the treatment and control group.

This study's results showed that both control and intervention group experienced improvement of VAS in neck, shoulder, upper back and lower back pain, although there were no statistical significances for delta VAS of neck, upper and lower back pain. The delta VAS in shoulder pain and VAS for lower back pain in intervention compared with control group, were reduced significantly and showed that E-BACKNSHOU with 20-20-20 exercise could improved extra ocular symptoms of CVS.

The limitation of this study is the short intervention time, only about 1 month, and the limited number of participants. The participants all came from the same department (Faculty of Medicine of Diponegoro University). So, further research with more intervention duration, more participants with more varieties of department or university can be implemented.

CONCLUSION

Shoulder and low back pain were decreased by performing the 20-20-20 rule and E-BACKNSHOU exercises rather than the 20-20-20 rule only.

The 20-20-20 rule and E-BACKNSHOU exercises can be used in CVS patients with neck, shoulder, and back pain.

Future studies can use control group with the same characteristics (using exercise) rather than 20-20-20 rule only and longer duration (more than 4 weeks). E-BACKNSHOU exercises can be studied with larger sample and more detailed inclusion criterias.

Expression of Gratitude

The researcher would like to thank students of Faculty of Medicine, Diponegoro University, Semarang who have been willing to become research subjects, and also other parties that have helped the process of this research up till the writing of this article so that it can be conducted successfully.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 94–99

OPEN ACCESS

Original Article

Prenatal, Perinatal and Postnatal Risk Factors from Mother and Child to The Incidence of Epilepsy

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1042

Accepted: October 30th, 2023
Approved: March 20th, 2024

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Publisher's Note:
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Abstract

Background : Epilepsy is a health problem that affects sufferers and their families, characterized by at least two seizures without provocation with an interval of more than 24 hours between seizures, one seizure without provocation with the possibility of recurring within 10 years, a diagnosis of epilepsy syndrome has been established. The risk of epilepsy can be influenced by the condition of the mother and child in the prenatal, perinatal and postnatal periods. This study analyzed the risks of several prenatal, perinatal, and postnatal factors of mother and child as risk factors for epilepsy incidence.
Methods : A case control study was conducted at RSUP Dr. Kariadi Semarang from July 2022 to March 2023. A total of 90 eligible subjects were divided into 45 case with epilepsy and 45 control with a non-epileptic diagnosis. Inclusion criteria were aged over 17 years to 40 years and exclusion criteria were subjects with mothers who had died or could not be interviewed, data were incomplete and had structural brain disorders or other diseases with clinical symptoms of seizures for the control group. The data obtained were analyzed using chi squares test for bivariate association, followed by multivariate analysis with multiple logistic regression.
Results : Maternal age during pregnancy (p=0.016), low birth weight (p=0.007), surgical birth (p=0.004), head trauma at the age of less than 6 years (p=0.008) have been shown to influence the occurrence of epilepsy with significance respectively.
Conclusion : Prenatal factors of the mother which is maternal age during pregnancy, perinatal and postnatal factors of the child which are low birth weight, surgical birth, and head trauma at the age of less than 6 years are risk factors that influence the occurrence of adulthood epilepsy.

Keywords : Adulthood epilepsy, prenatal, perinatal, postnatal, risk factors.

INTRODUCTION

Epilepsy is one of the prominent health problems in society, because the problem is not only from a medical perspective but also from a social and economic perspective that affects subjects and their families. Epilepsy does not occur due to a single cause. There are several factors that can damage brain cells or interactions between brain cells.[1] The factors that have been widely studied are the perinatal conditions of individuals with epilepsy. However, another thing that needs to be investigated is the mother's factor during prenatal conditions. The medical condition of the mother influences the nature of the condition in utero (environment) which regulates brain development in the offspring that are born. When information about environmental is examined, it can provide important clues about how the mother's medical complications affect the developmental trajectory of the child's brain.[2]

METHODS

The research conducted was an analytic observational study using a case control design at RSUP Dr. Kariadi Semarang in the period July 2022 to March 2023. Research subjects were selected based on epilepsy (ICD-10 G40) and non-epilepsy diagnoses (ICD-10) obtained from medical records, then tracing was carried out on the patient's mother whether she had the risk factors being studied or not by telephone or home visit. This study involved 90 subjects, with 45 cases and 45 controls. The inclusion criteria for both groups were subjects with age 17–40 years old. Exclusion criteria for both groups were subjects whose mothers had died or could not be interviewed and data were incomplete, with additional criteria for control group of had structural brain disorders or other diseases with clinical symptoms of seizures (acute symptomatic seizure). Furthermore, interviews were conducted using a questionnaire with the subject's mother directly, by telephone or home visit to obtain research variable data. The data obtained were analyzed using univariate analysis for subjects characteristics, Chi-Square and Odd Ratio as bivariate analysis, and multiple logistic regression analysis as multivariate analysis.

RESULTS

This study involved 90 subjects who met the inclusion criteria, with 45 in case group and 45 control group. The characteristics of the research subjects were presented in Table 1.

In this study, the mean age in control group was older than the mean age of case group. There were more males than females in both case and control groups. The educational level of both groups were mostly senior high school. There was 1 case subject who was born to a grand multipara mother (number of parities > 4). There was no difference between the case and control groups, so it can be assumed that demographic characteristics were similar between two groups.

Table 2 showed that there was no difference in the mean age of the mother and the parity status of the mother between the case and control groups. Based on the age category of the mother during pregnancy, it was found that mothers with vulnerable age for pregnancy was more likely found in the case group. Based on statistical analysis, subjects born to mothers at a vulnerable age to get pregnant have 8.734 times higher risk of experiencing epilepsy.

A history of preeclampsia during pregnancy was only found in the case group. Mother was asked whether

TABLE 1
Demographic Characteristics of the subjects

		Epilepsy	Non epilepsy	*p*
Mean age (in years)		25.71 (6.43)	31.38 (5.682)	0.152
Gender; n (%)	Male	24 (53.3%)	24 (53.3%)	1.0
	Female	21 (46.7%)	21 (46.7%)	
Education level	Special school	3 (6.7%)	0 (0%)	0.13
	Elementary school	3 (6.7%)	1 (2.2%)	
	Junior high school	6 (13.3%)	4 (8.9%)	
	Senior high school	22 (48.9%)	20 (44.4%)	
	Diploma/bachelor	11 (24.4%)	20 (44.4%)	
Parity of subject's mother	≤ 4	44 (97.8%)	45 (100%)	1.0
	> 4	1 (2.2%)	0 (0%)	

TABLE 2
Characteristics of mother during pregnancy

Characteristics of mother		Group		*p*	OR
		Epilepsy	Non epilepsy		
Parity status	Parity 1–4	44 (97.8%)	45 (100%)	1.0	
	Parity ≥ 5	1 (2.2%)	0 (0%)		
Mean maternal age during pregnancy (in years)		27.8 (7.42)	28.89 (3.588)	0.87	
Categories of maternal age during pregnancy	20–35 years old	32 (71.1%)	43 (95.6%)	0.005	8.734
	<20, >35 years old	13 (28.9%)	2 (4.4%)		
Preeclampsia	No	33 (73.3%)	45 (100%)	0.01	2.364
	Yes	12 (26.7%)	0 (0%)		
History of systemic infection during pregnancy	No	38 (84.4%)	43 (95.6%)	0.160	
	Yes	7 (15.6)	2 (4.4%)		

TABLE 3
Characteristics of subjects at birth

Characteristics of subjects at birth		Epilepsy	Non epilepsy	*p*	OR
Gestational age at birth	Full term	40 (88.9%)	43 (95.6%)	0.431	
	Premature	5 (11.1%)	2 (4.4%)		
The process of birth	Normal	35 (77.8%)	43 (95.6%)	0.03	6.143
	With procedure	10 (22.2%)	2 (4.4%)		
Birth weight	Normal	33 (73.3%)	44 (97.8%)	0.03	16
	Low birth weight	12 (26.7%)	1 (6.5%)		
Asphyxia	No	37 (82.2%)	45 (100%)	0.01	2.216
	Yes	8 (17.8%)	0 (0%)		

there was high blood pressure started on second trimester accompanied by abnormal blood and urine examination which caused mother was hospitalized, or whether mother had been diagnosed with preeclampsia. There was no history of preeclampsia in the control group. Based on statistical analysis, subjects born to mothers with preeclampsia during pregnancy had a 2.364 times higher risk for experiencing epilepsy.

A history of maternal systemic infection during pregnancy was more common in the case group. Mother was asked whether mother had fever during pregnancy which led to inpatient with abnormal blood examination or whether mother had been diagnosed with infection during pregnancy. Based on statistical analysis, there was no difference between the case and control groups.

Table 3 showed that based on the category of maternal gestational age when the subjects were born, most of the subjects were born at term, and based on statistical analysis, there was no significant difference between the two groups.

Based on the category of birth process, most of subjects were born with normal delivery. Labor with procedure such as caesarean section (SC) and vacuum extraction were more common in the case group. There were no subjects with a history of birth with forceps extraction in both groups. Based on statistical analysis, subjects who were born with surgical or assisted deliveries had a 6.143 times higher risk of experiencing epilepsy.

Based on the category of birth weight, more subjects were born with low birth weight in the case group. Based on statistical analysis, subjects born with low birth weight have a 16 times higher risk for developing epilepsy.

Subjects who were born with asphyxia were only found in the case group. Mother was asked whether the

TABLE 4
Characteristics of patient at postnatal

Characteristics of patient at postnatal		Epilepsy	Non epilepsy	*p*	OR
History of head trauma (before seizure onset)	No	37 (82.2%)	44 (97.8%)	0.035	9.514
	Yes	8 (17.8%)	1 (2.2%)		
Neonatal infection	No	39 (86.7%)	45 (100%)	0,035	2.429
	Yes	6 (13.3%)	0 (0%)		

TABLE 5
Multiple logistic regression analysis on risk factors for epilepsy

Variable	*p*	Adjusted OR
Maternal age during pregnancy	0.016	1.149
Birth with procedure	0.007	15.854
Low birth weight	0.004	36.774
History of head trauma	0.008	36.656

patient did not cry immediately when he/she was born, had a slow breathing rate, pale or blue skin, or a history of intensive care immediately after birth. If the patient was born at home or midwife, there was a history of being referred to hospital for intensive care. There was no history of asphyxia in the control group. Based on statistical analysis, subjects born with asphyxia have a 2.216 times higher risk of experiencing epilepsy.

Table 4 showed that a history of head trauma which is a hard impact to the head or from a height of ± 1 meter which cause the patient to be hospitalized with or without impaired consciousness was more common in the case group. Based on statistical analysis, subjects who had a history of head trauma with a height of ± 1 meter have a 9.514 times higher risk of experiencing epilepsy.

A history of infection as a neonate obtained from mother which was characterized by fever that caused hospitalization or diagnosed with infection within the first four weeks of life was only found in the case group. There was no history of neonatal infection in the control group. Based on statistical analysis, subjects who had a history of neonatal infection were 2.429 times more likely experiencing epilepsy.

Table 5 showed that variables of maternal age during pregnancy, birth procedure, low birth weight, and history of head trauma partially (separately) influence the incidence of epilepsy. The most influence variable in this study was low birth weight, where subjects born with low birth weight had a 36.774 times greater risk for experiencing epilepsy later in life.

DISCUSSION

In this study, maternal parity status which was divided into non-grand multipara (parity 1–4) and grand multipara (parity ≥ 5) did not prove to be significant as a risk factor for epilepsy. This could be because of the total case and control subjects, there was only 1 subject who came from a mother with a parity of ≥ 5. This can be influenced by increased family awareness regarding family planning programs and the introduction of contraception. So now it is rare to find mothers with children ≥5.

Based on the age category of the mother, most of them are the age group of 20–35 years which is a safe age for pregnancy. In this study, subjects born to mothers at a vulnerable age for pregnancy, namely < 20 years and > 35 years, had an 8.734 times greater risk of experiencing epilepsy. Mothers who get pregnant at an older age often suffer from diseases such as hypertension, eclampsia, cervical cancer, diabetes and heart disease.[3] Hypertension, eclampsia, and diabetes may lead to various structural and functional changes of placenta and impaired vascularization during pregnancy, even leading to preterm birth and abortion. Heart disease affects the mother's strength to push during labor, which can lead to hypoxia or asphyxia to the baby. Cervical cancer can cause birth canal disturbances that cause prolonged labor and hypoxia to the baby. These conditions can lead to epileptogenesis.[3] At older age, the birth canal is less elastic than before, resulting in difficult and long labor. This is coupled with decreased strength of

mother to expel the baby due to age and concurrent comorbidities. This condition may cause asphyxia and/or experience birth trauma in the form of intracranial bleeding which can progress to epilepsy in the future.[4]

Based on bivariate analysis, pregnancy with preeclampsia is a risk factor for epilepsy. Bivariate analysis found that subjects born from mothers with preeclampsia have a tendency to experience epilepsy. However, after multivariate analysis, preeclampsia was not statistically significant as a risk factor for epilepsy. This could be due to several risk factors influencing one another in their contribution to the incidence of epilepsy. This effect is further reduced in multivariate analysis.

In this study a history of systemic infection in the mother during pregnancy was not proven to be statistically significant, either simultaneously or partially as a risk factor for epilepsy. This is not in accordance with cohort research previously by Whitehead E who followed the progress of the patient from 1986 to 2001, it was found that infection during pregnancy in the mother is a factor that increases the risk of developing epilepsy.

Bivariate analysis found that subjects born prematurely had a tendency to experience epilepsy. However, after multivariate analysis, premature birth was not statistically significant as a risk factor for epilepsy. This could be due to several risk factors influencing one another in their contribution to the incidence of epilepsy. This effect is further reduced in multivariate analysis. In this study, only 7 subjects were born prematurely. This is in accordance with research by Tri Budi Raharjo in 2007. Different with previous research by Wanling Li et al in 2019 which showed premature birth as a significant risk factor for epilepsy.[5] This result may be due to the fact that children born prematurely may still experience optimal brain development according to their age and have sufficient birth weight, thus indicating that organ development is viable enough, including the brain. Based on research by Yuelian Sun in 2007 it was found that among children who were born prematurely, only children who had lower birth weight below the 5th percentile Z score had higher incidence rate ratio of epilepsy than children with birth weight above the 15th percentile Z score.[6] In addition, this can also be influenced by the nutritional conditions given to subjects who were born prematurely, to catch up on brain development so that it can be optimal.[7]

Based on multivariate analysis, subjects who were born with a history of labor with action, either cesarean section or vacuum extraction have a 15.854 times higher risk of having epilepsy. These factors are related to prolonged labor and labor with action, and are thought to be related to cephalopelvic disproportion.[8] The incidence of seizures and encephalopathy is nearly double in infants born by vacuum extraction after >41 weeks gestation, compared with 39–41 weeks gestation. Mothers with dystocia can be assisted in delivery procedures, both vacuum extraction and SC, but babies born from vacuum extraction are exposed to higher risks, both in terms of duration and pressure (from the vacuum device) during the delivery process itself.[9]

Based on the multivariate analysis test, subjects who were born with low birth weight had a 36.774 times higher risk of experiencing epilepsy. Infants born with low birth weight may soon experience hypoxic ischemia and/or intraventricular haemorrhage, with clinical manifestations in the form of seizures. This situation, can develop into epilepsy later in life.[3]

The perinatal risk factor that was also studied was asphyxia. From the bivariate analysis it was found that subjects born with asphyxia have a tendency to experience epilepsy. However, after multivariate analysis, perinatal asphyxia was not statistically significant as a risk factor for epilepsy. This may be due to several risk factors influencing one another in their contribution to the incidence of epilepsy. This effect is further reduced in multivariate analysis. In this study, only 8 subjects were born prematurely. This is in accordance with research conducted by Supriadi, perinatal asphyxia is not significant as a risk factor for epilepsy.[10] This could be due to the bivariate analysis of several risk factors influencing each other in their contribution to the incidence of epilepsy.

Based on statistical analysis, a history of head trauma was a risk factor that can increase the risk of up to 10.884 times the incidence of epilepsy. The impact that is not significant gives sequelae in the form of scar tissue, which does not give early clinical symptoms but within 3–5 years it will become the focus of epilepsy.[11] Although the head injury is less severe, the chance of having an epileptic seizure is higher in children than in adults.[12]

Bivariate analysis found that subjects with a history of neonatal infection had a tendency to experience epilepsy. However, after multivariate analysis, neonatal infection was not statistically significant as a risk factor for epilepsy. This could be due to several risk factors influencing one another in their contribution to the incidence of epilepsy. This effect is further reduced in multivariate analysis. In this study, only 6 subjects were born prematurely.

This research has weaknesses, among others, there are possibilities recall bias because this study used a retrospective case-control design. In addition, there is limited information in medical records and not all respondents had medical records during pregnancy and childbirth.

CONCLUSION

In this study, it was found that the age of the mother during pregnancy, low birth weight, assisted birth, and head trauma at the age of <6 are risk factors for epilepsy

both simultaneously and separately. Therefore prenatal, perinatal and postnatal factors from mother and child together and individually have been proven as risk factors that influence the occurrence of epilepsy.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 100–106

OPEN ACCESS

Original Article

Functional Capacity COVID-19 Survival among Workers in Koja Public Health Center

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Abstract

Background : Coronavirus disease 19 (COVID-19) primarily affects the respiratory system and other organ systems which limit respiratory and physical status. The aim of this study is to evaluate functional capacity COVID-19 survivor among workers in Koja Public Health Center
Methods : participant were enrolled on March–April 2022. Demographics, symptoms, functional scale post COVID-19 questionnaire, risk stratification, and 6-min walk test (6mwt) were analysed. Patients unable to walk were excluded from the study.
Results : 79 participants, 38% was a health care worker, had a median age 33 (21–57) years and 43 women (54.4%). Men had higher 6mwt 518.2 (120–625.8) meter while women had 457 (340–600) meter p (<0.001), VO2max 17.47 (9.74–20.67) in men and 16.45 (14.07–19.19) in women p (<0.001), and METs 5.02 (2.78–5.90) in men and 4.69 (4.02–5.48) in women p (<0.001). Most of the participant had good fitness, 10 participant (12.7%) had functional limitation; 2 participants (2.5%) still had symptom.
Conclusion : Despite being COVID-19 survivors, the workers at the Koja Public Health Center have good functional capacity.

Keywords : COVID-19, survival, Functional capacity, worker, 6mwt

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.942

Accepted: March 29th, 2023
Approved: March 20th, 2024

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INTRODUCTION

Coronavirus disease 19 (COVID-19) is a disease due to novel coronavirus SARS-CoV-2 virus that primarily affects the respiratory system and other organ systems.[1] World Health Organization (WHO) declared the situation as a Public Health Emergency of International Concern, and it was finally stated a global pandemic on March 11, 2020.[2] SARS-CoV-2 is an enveloped single-stranded RNA beta-coronavirus which is highly contagious. SARS-CoV-2 can spread directly through droplet and human-to-human transmission and indirectly by contact with contaminated objects and airborne contagion.[1] COVID-19 could affect respiratory status, physical and mental health.3 There are a wide range of symptoms in the infected SARS-CoV-2 patients. It can be ranges from minimal symptoms to severe respiratory failure with multiple organ failure.

COVID-19 could leave some sequelae after infection. Patients with severe COVID-19 disease may have some sequelae that could affect their respiratory status, physical and mental health after hospital discharge.[3] Many patients experience persistent respiratory symptoms months after their initial illness of COVID-19.[4] COVID-19 survivors are reported to have permanent lung damage, as a result of diffuse alveolar damage during the development of the disease.[5] There is also some emerging research to suggest that even mild to moderate COVID-19 can have negative ongoing functional associations for non-hospitalized patients.[6] Notably, also a considerable proportion of low-risk individuals with mild COVID-19 experience prolonged symptoms affecting work, social, and home life.[7] Based on the individual deficits in COVID-19 patients, comprehensive and multidisciplinary rehabilitation such as pulmonary rehabilitation should be offered with attention to improving respiratory, physical and psychological impairments.[8]

Measuring COVID-19 disease severity in a population has been important for understanding the public health impact of each variant of concern. A watershed moment in the COVID-19 pandemic was the emergence of the Omicron (B.1.1.529) variant of SARS-CoV-2 with widespread reports of lower disease severity relative to previous variants such as Delta (B.1.617.2). The case fatality ratio of 3.4% for Delta and 1.9% for Omicron, about a twofold difference. Therefore, Omicron does have lower severity by these measures, with the precise severity drop relative to Delta dependent on how the number of infections is estimated.[9]

We hypothesized that individuals with confirmed COVID-19 likely to have problems with physical capacity. This study conducted to investigate the physical capacity of non-hospitalised patients with COVID-19.

METHODS

Study design

This study was a cross-sectional clinical study on COVID-19 survivors among workers in Koja Public Health Center from March to April 2022. Koja Public Health was chosen as it is one of university partners in community engagement that had covid-19 cure and death percentages in the average range.

Subjects

Participants were recruited with consecutive sampling. The inclusion criteria of the study were aged ≥18 years, negative COVID, hemodynamically stable, respiratory rate <25 breath/min. The patients were excluded from the study if they have neurological, neuromuscular, and musculoskeletal limitations, cognitive dysfunction, end-stage of chronic diseases, and body mass index (BMI) >35 kg/m^2. All patients were instructed to sign a written informed consent after explanation about the details of the study procedures. Koja Public Health Center is managed and financed by the local government, under the DKI Jakarta Provincial Health Service.

Outcome measures

Patient characteristic, clinical symptoms were collected. Post covid-19 functional status scale (PCFS), risk stratification, fitness level and six minute walk test (6MWT) were assessed. Post covid-19 functional status scale was a questionnaire covering the entire range of functional limitations, including changes in lifestyle, sports, and social activities. If there was no limitation of activity, it was graded as Grade 0, if there was a negligible effect on activities for patients was considered Grade 1, whereas a lower intensity of the activities was considered as Grade 2. Grade 3 accounted for the inability to perform certain accomplishments, forcing patients to structurally modify these. Finally, Grade 4 was reserved for those patients with unembellished functional restrictions.[10] Risk stratification consist of symptom, activity and medical condition of subject. If there was a symptom, it was graded as A, if there was no symptom, active, without medical condition it was graded as B, if there was no symptom, active, with medical condition it was graded as C, if there was no symptom, not active, without medical condition it was graded as D, and if there was no symptom, not active, and with medical condition it was graded as E. 6MWT is simple, easy to perform, inexpensive and widely used in clinical routine provides a useful assessment tool of cardiopulmonary and musculoskeletal function that is relevant to daily activities.[11] Using Cahalin formula to predict VO2max from the 6MWT for measuring aerobic exercise capacity.[12]

Statistical analysis

All data were analysed using SPSS version 20. The data were checked for normal distribution by the Shapiro-Wilk test. Data were analysed based on a T-test analysis method to determine the differences between gender and occupation if data normally distributed and Mann Whitney if data non normally distributed. The significance level was set at P<.05 for all outcome measures.

RESULTS

Seventy-nine recovered COVID-19 subjects were enrolled in this study, 36 (45.6%) were men and 43 (54.4%) were women. The median age was (21–57) years. In Thirty subjects (38%) were a health worker which included doctors, dentists, nurses, midwife, physiotherapists, etc; and forty nine subject (62%) were non health worker which included administrations, security, driver, etc (Figure 1).

Ten (12.7%) subjects had functional limitation after COVID-19 infection. The functional state of subject consists of sixty-nine (87.3%) subjects had grade 0, one subject hade grade 1 and nine subjects had grade 2 (Figure 2). Two (2.5%) subjects still had symptom after negative COVID-19 (Figure 3). The 6MWT of the COVID-19 survivors were 487.5 (120–625.8) meter, with VO2max 17(9.74–20.67) and METs 4.84 (2.78–5.9). The

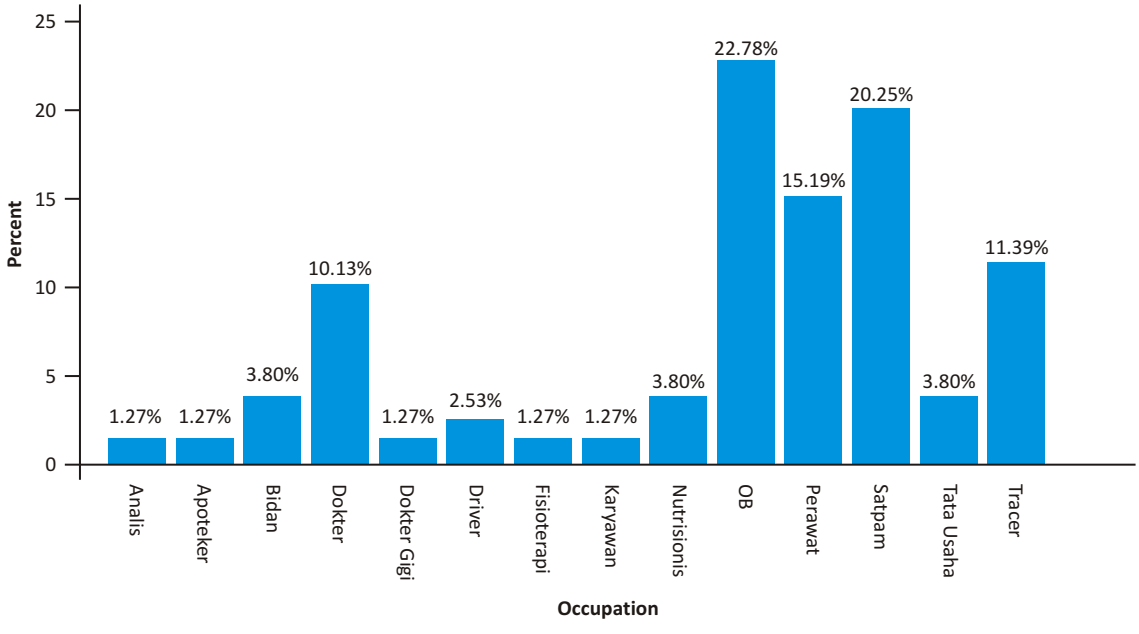

Figure 1. Type of Occupation

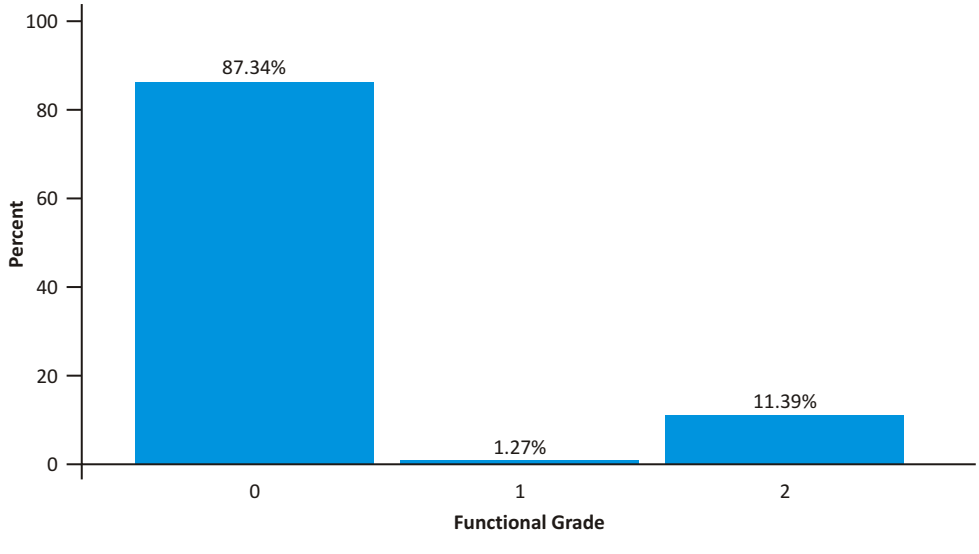

Figure 2. Functional Grade

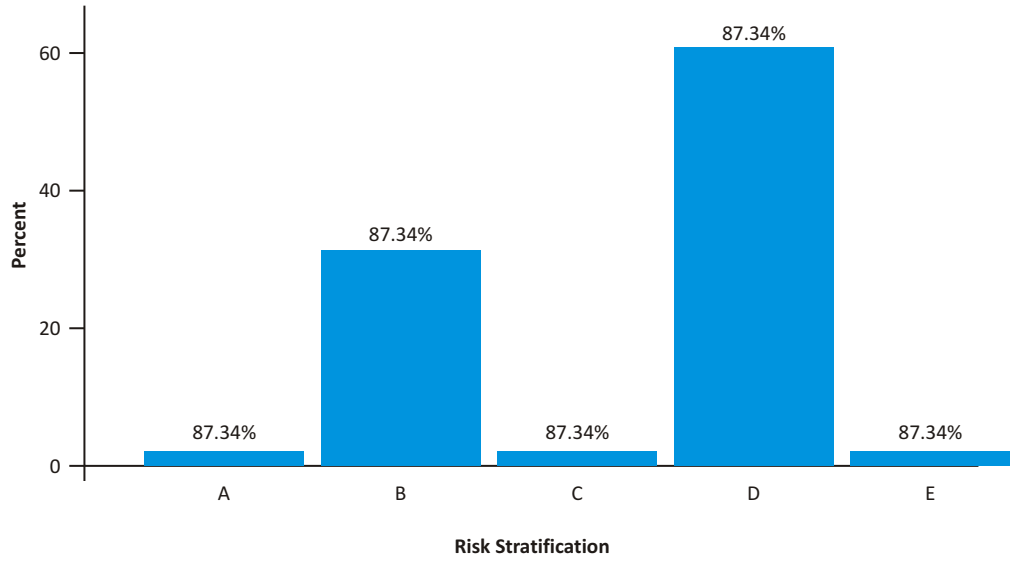

Figure 3. Risk Stratification

TABLE 1
Functional Capacity

Variable		Subject (n=79)	p
6MWD (m)	Men (n=36)	518.2 (120 – 625.8)	<0.001*[a]
	Women (n=43)	457 (340 – 600)	
Vo2max (ml/kg/min)	Men (n=36)	17.47 (9.74 – 20.67)	<0.001*[a]
	Women (n=43)	16.45 (14.07 – 19.19)	
METs	Men (n=36)	5.02 (2.78 – 5.90)	<0.001*[a]
	Women (n=43)	4.69 (4.02 – 5.48)	

*p<0.05=Significance, [a]Mann Whitney

median 6MWD, VO2max and METs was significantly lower in women (P <0.001) is presented in Table 1. Only one subject (1.3%) had poor level fitness (1,5–3 METS) and seventy-eight (98.7%) had moderate level fitness (3–6 METS). There was no significant different among health worker when compare with non-health worker for 6MWD (p=0.538), VO2max (p=0.443) and METs (p=0.430).

DISCUSSION

COVID-19 causes a wide range of pulmonary and extrapulmonary clinical symptoms, including functional capacity impairment. (e.g., muscle weakness, mobility decline, reduced exercise tolerance, circulatory limitation, lung damage, and myopathy). Previous experience with SARS, another severe viral respiratory syndrome comparable with COVID-19, suggests that patients with this illness have experienced varying degrees of abnormalities in their muscle capabilities, quality of life, and cardiorespiratory after a year of follow-up. In fact, as many as 23.7% showed a decreased exercise capacity after a year of hospital discharge, compared to the predicted levels for age-matched healthy adults. Vianna *et al* found lower levels of 6MWT distance (~21%) and percentage of predicted 6MWT distance (~20%). The multisystemic nature of COVID-19 could be one possible theory. The performance of functional tests not only dependant by the respiratory system, but also the integration of multiple physiologic systems. The combined effects of detraining and COVID-19 sequelae may limit exercise capacity, and both leg muscles and respiratory are susceptible to a variety of systemic illnesses that reduced strength and mobility. Anaemia and myopathic changes were found to be the primary causes of reduced exercise capacity rather than pulmonary, respiratory, cardiac impairments, or vascular on the day before hospital discharge in previous

studies of COVID-19 pneumonia survivors. In line with the role of peripheral factors on exercise capacity, the most common persistent symptoms are fatigue or muscle weakness (63%) after 6 months COVID-19 onset. The combined effect of COVID-19 symptoms and detraining was predicted to alter the arousal of post viral fatigue syndrome, hence effecting exercise capacity.[13]

6MWD was performed to assess the global and integrated responses to exercise.[14] Age, gender, race, height, and weight were all statistically significant predictors of 6MWD.[15] In this study Men had higher 6MWD 518.2 (120–625.8) meter while women had 457 (340–600) meter p (<0.001), VO2max 17.47 (9.74–20.67) in men and 16.45 (14.07–19.19) in women p (<0.001), and METs 5.02 (2.78–5.90) in men and 4.69 (4.02–5.48) in women p (<0.001). Given that taller people tend to take longer steps, which makes walking more efficient and allows for greater distances to be covered by taller women and men.[15] Walking distance cut off points were examined between genders. In male subjects, actual walking distance were taken as normal if it was greater than 483 meters, poor if it was 434–483 meters, and very poor when less than 434 meters. As for female subjects, normal when greater than 442 meters, poor when 405–442 meters, and very poor in distance when less than 405 meters.[16] Based on the cut off value, it may be assumed that, on average, the majority of functional participants are in excellent condition.

Most age groups had low 6MWT distance, myopathy and muscular wasting might be responsible for this, since most of COVID-19 survivors had a very well-preserved lung function. Muscle loss and physical deconditioning may result from extended bed rest and hospitalization. In addition, medication using systemic corticosteroids might contribute to myopathy.[14] In older study, found that the 6MWT distance of the 21 (80.7%) test subjects from the COVID-19 group (561.1 ± 71.0 m) was lower than the controls (652.6 ± 53.4 m), ($p < 0.05$).[17] The COVID-19 Group's SpO2 measured during the 6MWT was substantially lower, and their measurements of leg fatigue, general fatigue, and dyspnea scores were all significantly greater. Severe COVID-19 patients have persistent lung damage that lowers their functional capability, quality of life, and respiratory function. According to Ferrandi *et al* hint that covid-19 virus may affect some skeletal muscle through angiotensin-converting enzyme-2 (ACE-2). While the SARS-COV 2 is active in the lungs and leukocytes infiltrate the lung tissue, these leukocytes produced cytokines (most notably IL-6) which disrupts metabolic homeostasis and causes muscle loss by entering and infiltrating into the muscle. Furthermore, inadequate oxygen diffusion and delivery to peripheral tissues, due to fibrosis could explain peripheral muscle weakness. All these explanations about declining strength of the peripheral muscles could be the cause of shorter 6MWT distance.[17]

Different with previous studies, we found only two subjects still had symptom after negative COVID-19 and only one subject had poor level fitness. Most of subject had moderate level fitness (3–6 METS), and 87.4 % had grade 0 functional capacity (Figure 2), which means they do not have activity limits despite being exposed to COVID-19. This condition may be due to all subjects had mild symptom and non-ARDS patients. Anastasio *et al* found correlation between SpO2/FIO2 ratio and SpO2 at rest ($p<0.001$) and during 6MWT ($p<0.001$) was higher in non-ARDS patients.[18] Furthermore numerous studies finds no evidence of Omicron having lower severity than Delta, as determined by the percentage of positive test-takers who report symptoms or the percentage of individuals who seek medical treatment after the infection. However, currently there are relatively little hospitalization data available.[19] The lower disease severity observed populations during the Omicron wave of the SARS-CoV-2 pandemic infection can be attributed to mutations in the virus that limit its ability to spread in the lungs and, probably most importantly, to increased immunity in the population by COVID-19 vaccination and also, previous infection. The severity of the disease is measured by the outcomes such as the need for additional ventilation, supplemental oxygen, total hospital admissions, and mortality. This results in a case fatality ratio of 1.9% for Omicron and 3.4% for Delta, which about two times of a difference. As a result, Omicron does have lower severity compared with Delta depending on how the COVID-19 infection is estimated.[9] Limited information regarding the type of variant and onset of COVID 19 in each participant is a weakness in this study. As a result, the analysis of the correlation between the COVID-19 variation and the level of fitness cannot be conducted.

Among the findings of this study, 60.76% (Figure 3) of participants were classified as stratification grade D, which implies they have no symptoms and no history of disease but are not physically active. This is especially concerning because a lack of physical exercise raises the risk of chronic diseases such as cardiovascular disease, metabolic disorders, and other cognitive disorders.[20] Furthermore, being in a condition of passive activity, particularly during the COVID-19 epidemic, can increase the occurrence of depression, stress, and anxiety. As a consequence, it is essential to empower people to maintain physical activity.[21] Unfortunately, there was no details on prior activity history in this study. As a result, we cannot determine whether this inactivity is related to Covid19 or has been in the past.

CONCLUSION

The functional capacity and health status of COVID-19 survivors was good in workers in Koja Public Health Center. The lack of data on the onset of covid, the number

of times exposed to covid, and the level of fitness prior to covid were weakness in this study. There for, further research is recommended, using better design.

Abbreviations

COVID-19 : Corona Virus Disease 2019, 6MWT : 6 Minute Walking Test, METs : Metabolic Equivalents, WHO : World Health Organization, RNA : Ribonucleic Acid, BMI : Body Mass Index, PCFS : Post Covid 19 Functional Scale, SPSS : Statistical Package for the Social Sciences,6MWD :The 6-min walk distance,SPO2 :peripheral capillary oxygen saturation, ACE 2 : Angiotensin-converting enzyme 2,IL-6 : Interleukin 6,ARDS : Acute respiratory distress syndrome.

Ethics Approval and Consent to Participate

The study was approved by the Medical Faculty of University Indonesia Research Ethic Committee.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

The datasets generated and/or analysed during this study are not publicly available due to confidentiality but are available upon reasonable request.

Authors' Contribution

IM was the project leader and was responsible for study and project design. MH, WK PS, BL, N, and RK as conceptualized designs and as advisers. RE, ED, VN, and PO performed the data collection. AD, RZ, RF, and FL calculated the study results. NS, ES, SP and JT contribute in coordinating with research sites and assisting in data collection LM, YT, and GR were co-writing and involved in the revision of the manuscript.

Acknowledgment

The author would like to thank various parties; D.K.I Jakarta Provincial Health Office, North Jakarta Sub-dept., Koja District Public Health Center. the authors are also grateful for their contributions - the director and staff of the Cipto Mangunkusumo Hospital, and all parties involved in Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Indonesia.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 107–112

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Original Article

Effect of Triamcinolone Trigger Point Injection on Changes in TNF-α Levels and Oswestry Disability Index (ODI) Scores Non-Specific Low Back Pain (LBP) Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.976

Accepted: June 14th, 2023
Approved: March 20th, 2024

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Abstract

Background : Low back pain (LBP) is the most common musculoskeletal problem and a major cause of worldwide disability causing increased health costs and indirect costs associated with reduced or lost productivity. One of the therapeutic management of LBP is Triamcinolone trigger point injection. Until now, research on the effect of Triamcinolone trigger point injection on changes in TNF-α levels and Oswestry Disability Index (ODI) scores in Non-Specific LBP patients is still limited. The objectives of this study was to analyze the effect of Triamcinolone trigger point injection on changes in TNF-α levels and ODI scores before and after Triamcinolone trigger point injection in Non-Specific LBP patients.
Methods : This is a quasi-experimental analytic observational study with a pre and post-test group design approach. Subjects were diagnosed with Non-Specific LBP who had met the inclusion criteria (acute pain less than 3 months, patient age 30–55 years, moderate-severe pain intensity, had never received a Triamcinolone trigger point injection) with the exclusion criteria patients experiencing severe pain. not only caused by NPB. The study subjects were checked for TNF-α levels and ODI scores before and after the Triamcinolone trigger point injection. Then a paired T-test was carried out.
Results : During the study period September – November 2022 at the Neurology Outpatient Polyclinic, RSUP Dr. Kariadi Semarang obtained 32 subjects. There was a significant difference between changes in TNF-α levels before and after Triamcinolone trigger point injection (p=0.000). There was a significant difference in ODI scores before and after the Triamcinolone trigger point injection (p=0.000). There was no significant relationship between the risk factors for gender, occupation, BMI, physiotherapy, and changes in TNF-α levels with changes in the ODI score.
Conclusion : There is a significant difference in changes in TNF-α levels and ODI scores before and after Triamcinolone trigger point injection.

Keywords : TNF-α, ODI, Trigger Point Injection, Triamcinolone

INTRODUCTION

Low back pain (LBP) is felt in the lower back area, which can be local pain, radicular, or both. A systematic review conducted by Fatoye *et al* found the prevalence and incidence of LBP ranged from 1.4 – 20.0% and 0.024 – 7.0%.[1] Data from 2017 The Global Burden of Disease (GBD) study found the number of individuals with LBP in 1990 was 377.5 million, and increased to 577.0 million in 2017.[2]

Based on the pathophysiology of low back pain is divided into specific and non-specific low back pain. Specific low back pain is a symptom caused by a specific pathological mechanism, such as herniated nuclei cause (HNP), infection, osteoporosis, rheumatoid arthritis, fracture, or tumor. Non-specific low back pain (Non-specific low back pain) is a symptom without a clear cause, the diagnosis is based on the exclusion of specific pathology. The word "non-specific" indicates that there is no clear structure that causes pain. Non-specific low back pain includes diagnoses such as lumbago, myofascial syndromes, muscle spasms, mechanical LBP, back sprain, and back strain.[3]

Non-specific low back pain is the main cause of increased morbidity, disability, and limited body activity.[4] LBP is a musculoskeletal condition that leads to limited activity with social and medical problems such as increased health costs and indirect costs related to reduced or lost productivity.[5]

The primary function of TNF-α is to regulate the activity and gene expression of matrix metalloproteinase (MMP), decrease the synthesis of collagen and proteoglycan, trigger inflammatory responses, and promote the production of other cytokines such as IL-1, IL-6, IL-8, and prostaglandin E2. It also aids in cell migration and improves endothelial cell permeability. The TNF-α released during the inflammatory process triggered by herniated intervertebral discs plays a role in causing mechanical and thermal hyperalgesia.[6]

One of the therapeutic management of LBP is the injection of corticosteroid trigger points. Triamcinolone is a synthetic corticosteroid that acts as an anti-inflammatory. Triamcinolone forms used are Triamcinolone Acetonide (TA) and Triamcinolone Hexacetonide (TH). Triamcinolone Acetonide inhibits proinflammatory cytokines and stimulates the release of anti-inflammatory cytokines. Triamcinolone Acetonide can suppress Tumor Necrosis Factor (TNF) Alpha, which is a pro-inflammatory cytokine. An important anti-inflammatory mechanism of Triamcinolone Acetonide is mediated by the inhibition of Nuclear Factor Kappa-B (NF-kappa-B), which causes decreased expression of the protein Tumor Necrosis Factor (TNF) Alpha.[7,8]

Until now, research on the effect of Triamcinolone trigger point injection on changes in TNF-α levels and Oswestry Disability Index (ODI) scores in non-specific low back pain (LBP) patients is still limited. The purpose of this study was to analyze the effect of Triamcinolone trigger point injection on changes in TNF-α levels and Oswestry Disability Index (ODI) scores before and after Triamcinolone trigger point injection in Non-Specific Low Back Pain (LIP) patients.

METHODS

This research is a quasi-experimental analytic observational study with a pre and post-test group design approach. The research was conducted at the Neurology Outpatient Polyclinic at RSUP Dr. Kariadi Semarang from September to November 2022. Inclusion criteria for this study were non-specific low back pain patients with acute pain less than 3 months, patients aged 30 – 55 years, moderate to severe pain intensity with a single trigger point, and patients who had never received Triamcinolone trigger point injection. Exclusion criteria in this study were patients experiencing pain that was not only caused by low back pain (known from history and physical examination).

The triamcinolone injection used in this study was 10 mg. The injection was carried out at the location of the trigger point using a 24 G needle with an injection perpendicular to the center of the active trigger point at one trigger point. In this study, the determination of trigger points was based on pressing the index finger of one doctor examining in the area suspected of having a trigger point and comparing it to the opposite side of the lower back.

Serum TNF-α level is an important inflammatory biomarker when inflammation occurs and is also found in inflammatory conditions such as LBP. Measurement with Elisa Kit (Enzym-linked Immunosorbent).

The ODI is a questionnaire used by health care providers to measure LBP outcomes, divided into 10 sections to assess limitations in various daily activities. Each section has a scale of 0–5, with 5 indicating the most severe disability. Calculated by dividing the total score by the normal total score, then multiplied by 100 and shown as a percentage. Improvement is marked by a decrease in the ODI score of> 10 points.

Data analysis using the "SPSS for Windows version 26" program. The first stage is a descriptive statistical stage to determine the basic characteristics of research subjects' gender, BMI, occupation, physiotherapy, ODI score, and TNF-α levels. The second stage is the Shapiro-Wilk normality test. Then a comparative test of TNF-α levels and ODI scores were carried out before and after injection of Triamcinolone trigger point by paired T-test and logistic regression test was performed to determine the relationship between changes in TNF-α levels, body mass index (BMI), gender, occupation and physiotherapy alone or together with changes in the Oswestry Disability Index (ODI) score of

Non-Specific low back pain (NPB) patients.

The confounding variables in this study consist of body mass index, gender, occupation, and physiotherapy. This research has received Ethical Clearance approval from the Research Ethics Commission at RSUP Dr. Kariadi with the number 1148/EC/KEPK-RSDK/2022.

RESULTS

The research was conducted from September to November 2022 at the Neurology Outpatient Polyclinic, RSUP Dr. Kariadi Semarang. During the study period, 84 subjects with acute non-specific low back pain (NPB) were observed, with 28 subjects with mild pain intensity so they did not receive Triamcinolone trigger point injections and 56 subjects receiving Triamcinolone trigger point injections with moderate to severe pain intensity, with 24 subjects of whom had more than one trigger point, and 32 subjects had moderate-to-severe pain intensity with VAS 6.34 ± 1.001 and had a single trigger point that met the inclusion criteria who were injected with Triamcinolone trigger points who participated in and completed the study. No subjects were excluded during the study and no research subjects were dropped out.

Based on Table 1, shows that research subjects who experienced Non-Specific low back pain were more common in women as many as 25 subjects (78.1%) compared to men as many as 7 subjects (21.9%). Research subjects with risky jobs have 17 subjects (53.1%) more than jobs that are not at risk, there are 15 subjects (46.9%). The study subjects who experienced Non-Specific low back pain were more obese as many as 18 subjects (56.3%) compared to those who were not obese as many as 14 subjects (43.7%).

Based on Table 2, shows that the mean TNF α level before injection of the Triamcinolone trigger point was 108.84 and the mean TNF α level after injection of the Triamcinolone trigger point was 45.24 which showed that with Triamcinolone trigger point injection there was a change in TNF α levels. After the paired T-test was carried

TABLE 1
Characteristics of research subjects

Variable		Frequency	Percentage (%)	Means (SD)	*p*
Gender	Man	7	21.9		0.468
	Woman	25	78.1		
Female	Risky	17	53.1		0.814
	No risk	15	46.9		
BMI	Obesity	18	56.3		0.468
	Not obese	14	43.7		
Physiotherapy	Physiotherapy	13	40.6		0.422
	Not Physiotherapy	19	59.4		
TNF α levels before injection trigger point				108.84 (136.19)	0.557
ODI score before injection trigger point				31.44 (5.33)	0.939

*P Test homogeneity (sig p>0.05)

TABLE 2
Changes in TNF-α levels, ODI, and VAS scores before and after Triamcinolone trigger point injection

Variable	Means (SD)			t	*p*
	Before	After	Change		
TNF α levels	108.84 (136.19)	45.24 (67.41)	64.44 (102.08)	4.136	0.000
ODI score	31.44 (5.33)	20.75 (5.68)	10.66 (5.84)	10.354	0.000
VAS	6.38 (1.04)	4.53 (1.13)	1.84 (1.11)	9.39	0.000

*P test paired T-test (sig p<0.05)

TABLE 3
Relationship between the location of the Trigger point injection and changes in VAS, changes in ODI scores, and changes in TNF-α levels

Variable		Trigger point injection location		P	r
		Lumbar paravertebral region	Gluteus region		
VAS changes	Still	4	4	0.703	0.073
	Down	14	10		
ODI Score Change	Getting better	11	10	0.712	0.107
	Not getting better	7	4		
Change TNF levels-α	Go on	3	4	0.669	0.141
	Down	15	10		

*P contingency coefficient test (sig p<0.05)

TABLE 4
Relationship between gender, occupation, BMI, and physiotherapy, and changes in TNF-α levels with changes in ODI scores

Variable		ODI score changes				P	B
		Getting better		Not getting better			
		n	%	n	%		
Gender	Man	5	15.6	2	6.2	0.235	1.791
	Woman	16	50.0	9	28.2		
Work	Risky	11	34.4	6	18.7	0.859	-.179
	No risk	10	31.3	5	15.6		
BMI	Obesity	16	50.0	2	6.2	0.080	3.306
	Not obese	5	15.6	9	28.2		
Physiotherapy	Physiotherapy	6	18.8	7	21.9	0.091	-1.990
	Not Physiotherapy	15	46.8	4	12.5		
Change TNF-α	Go on	4	12.5	3	9.4	0.750	-.418
	Down	17	53.1	8	25.0		

P Logistic Regression Test (sig p<0.05)

out, the results were obtained p = 0.000.

Based on Table 2, shows that the mean ODI score before the Triamcinolone trigger point injection was 31.44 and the mean ODI score after the Triamcinolone trigger point injection was 20.75, which shows that with Triamcinolone trigger point injection there was an improvement in the disability ODI score . After the paired T-test was carried out, the results were obtained p = 0.000.

Based on Table 3, shows that there is no relationship between the location of trigger point injection with changes in VAS, ODI score, and TNF-α levels, the results obtained are changes in VAS (p = 0.703), changes in ODI scores (p = 0.712), and changes in TNF-α levels (p = 0.669).

Based on Table 4, shows that there is no significant relationship between gender, occupation, BMI, and physiotherapy with changes in ODI scores. Gender (p=0.235), occupation (p=0.859), BMI (p=0.080), physiotherapy (p=0.091), and changes in TNF-α levels (p=0.750).

DISCUSSION

Research in determining trigger points, research conducted by Seyed Reza Saeidian *et al* in patients who have trigger points with the character of pain that arises after applying pressure of 2 kg/cm^2 on the area suspected of having a trigger point and comparing it with the

opposite side.[9] Research conducted by Bina Eftekharsadat in determining trigger points using a digital algometer (Wagner Instruments, Greenwich, CT, USA) to assess Pressure-pain threshold (PPT) at trigger points.[10–12] In this study did not use this tool, because the tool is not available in the hospital where the research is taking place, it is also very difficult to get the tool so it has the potential to affect research results.

In this study, changes in TNF-α levels were obtained, before and after injection of Triamcinolone trigger points. Changes in TNF-α levels were found in 10 subjects with normal range levels and 15 subjects with decreasing TNF-α levels, so a total of 25 subjects experienced changes in TNF-α levels with Triamcinolone trigger point injection. In this study, Triamcinolone trigger point injection was enough to show a statistical change in the initial decrease in TNF-α levels. This is to the study of Judith A Strong *et al* which stated that low back pain in patients is reduced by injection of corticosteroid trigger points. This is due to glial cell activation, macrophage infiltration, increased proinflammatory cytokines, and activation of inflammatory signaling pathways by lowering TNF-α levels. can reduce pain.[13] However, Andrade *et al*.'s study with a randomized clinical trial of TNF-α antagonists in radiculopathy patients failed to show a positive effect, because these trials tended to involve patients with chronic low back pain.[14] Triamcinolone is a steroidal anti-inflammatory drug, which has a tissue distribution that when injected has general anti-inflammatory effects, inhibiting type I inflammation (characterized by high levels of oxidative metabolites and proinflammatory cytokines) and enhancing type II inflammatory processes (tissue remodeling) and wound repair).[15] Risbud and Shapiro have investigated the relationship between cytokines and the development of pain. low back, where the association of low back pain begins with injury and is then followed by the release of TNF-α.[16] Triamcinolone Acetonide inhibits proinflammatory cytokines and stimulates the release of anti-inflammatory cytokines. Triamcinolone Acetonide can suppress Tumor Necrosis Factor (TNF) Alpha, which is a pro-inflammatory cytokine. An important anti-inflammatory mechanism of Triamcinolone Acetonide is mediated by the inhibition of Nuclear Factor Kappa-B (NF-kappa-B), which causes decreased expression of the protein Tumor Necrosis Factor (TNF) Alpha.[7,8]

Of the 32 subjects, a disability assessment was carried out with an ODI score before the Triamcinolone trigger point injection, then on day 30 a disability assessment was carried out with an ODI score after the Triamcinolone trigger point injection. Based on comparative test data on changes in ODI scores before and after Triamcinolone trigger point injections using the paired T-test, the results obtained were $p < 0.05$, so there was a significant decrease in ODI scores in patients before and after Triamcinolone trigger point injections. This is consistent with a study conducted by Bina Eftekharsadat *et al* showing that corticosteroid trigger point injections significantly reduced the ODI score of low back pain patients in the second week.[12] This is also in line with research conducted by Bahar Dernek *et al* which showed that in low back pain patients evaluated in the first month and third month it was found that the ODI score decreased after injection of Triamcinolone trigger point. to 32 patients for each group. After treatment with Triamcinolone trigger point injection, pain scores were reduced in the Triamcinolone trigger point injection group compared to the control group.[13]

There was no significant relationship between the location of trigger point injection and changes in VAS, ODI score, and TNF-α levels. The results showed changes in VAS ($p = 0.703$), changes in ODI scores ($p = 0.712$), and changes in TNF-α levels ($p = 0.669$). This is in contrast to a study conducted by Paul *et al*, which found that acute LBP patients experience changes in the structure and function of the back muscles which can be influenced by various biological and/or psychosocial influences. Biologics are associated with nociceptive pain, and afferent pain is associated with tissue injury. Intramuscular injection of hypertonic saline induces deep muscle pain and the appearance of musculoskeletal pain lasting 3 to 10 minutes. Changes in back muscle function during low back pain involving disturbed spinal posture control.

There is no significant relationship between changes in TNF-α and gender, occupation, BMI, and physiotherapy with changes in ODI scores. Gender ($p=0.235$), occupation ($p=0.859$), BMI ($p=0.080$), physiotherapy ($p=0.091$), and changes in TNF-α levels ($p=0.750$). Research by Park, *et al* found that the average TNF-α concentration was significantly higher in subjects who experienced chronic LBP intensity than in acute LBP. TNF-α is associated with pain quality and ODI.[19] A study by Uçeyleret *et al* found that there were two-fold higher levels of TNF-α in patients with LBP compared to healthy controls. In addition to its correlation with pain quality, TNF α has a positive correlation with ODI. Wanget *et al*' s study conducted a prospective comparative longitudinal study and found that there were much higher levels of TNF-α in the LBP patient group than in the control group.[20] Quieroz *et al*.'s study examined the relationship between TNF-α and ODI, which was positively correlated with disability due to LBP.[21]

RESEARCH LIMITATIONS

This study has limitations, namely, it does not take into account the measurability in determining trigger points in patients with non-specific low back pain and does not take into account the type and dose of painkillers consumed by patients before and during the study.

CONCLUSION

There was a significant difference between TNF-α levels before and after the Triamcinolone trigger point injection. There was a significant difference between the ODI score before and after the Triamcinolone trigger point injection. There was no significant relationship between age and location of trigger point injection with changes in pain intensity, TNF-α levels, and Oswestry Disability Index (ODI) scores. There was no significant relationship between changes in TNF-α levels, gender, occupation, BMI, and physiotherapy with changes in ODI scores after Triamcinolone trigger point injection.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 113–118

OPEN ACCESS

Case Report

Rehabilitation of A Child with Low Endurance in the Recovery Phase of Guillain-Barré Syndrome

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1020

Accepted: August 25th, 2023
Approved: December 28th, 2023

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Publisher's Note:
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Abstract

Background : Guillain-Barré Syndrome (GBS) usually has a good prognosis of recovery. However, some patients can have remaining disabilities due to low cardiorespiratory fitness or endurance and needs to be managed. This study was aimed to reports the rehabilitation assessment and management of a child with low cardiorespiratory endurance in the recovery phase of GBS.
Case : A 12-year-old girl with a history of hospitalization due to Acute Motor and Sensory Axonal Neuropathy (AMSAN)-type of GBS was referred to the Physical Medicine and Rehabilitation (PMR) outpatient clinic with tiredness that restricted her school participation. She had low cardiorespiratory endurance, which was confirmed by a six-minute walk test (6-MWT). After the rehabilitation program, her endurance level was increased, and she can return to school.
Discussion : A comprehensive assessment showed that the muscle weakness, accompanied by obesity, anemia, and inactivity, led to low cardiorespiratory endurance that restricted the activity and participation. A rehabilitation program that consisted of aerobic and strengthening exercises improved cardiorespiratory endurance, walking ability, and school participation.
Conclusion : Rehabilitation management in children with low cardiorespiratory endurance due to the sub-acute phase of GBS could help them regain their activity and participation during the recovery phase.

Keywords : Guillain-Barré Syndrome, endurance, rehabilitation

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an autoimmune disorder that targets the myelin sheaths of the nerve roots and peripheral nerves, resulting in myelopathy and neuropraxia.[1] It is considered a rare case, especially in the pediatric population.[2] The prognosis is typically good, with 70% of patients regaining functional status similar to the premorbid condition. However, about 20% of children have remaining disabilities after GBS.[1–3] Several studies reported that physical training in GBS patients also aimed to increase cardiorespiratory fitness.[4] Low cardiorespiratory fitness or endurance can lead to symptom of fatigue or tiredness that can interfere with activity and participation.[5] Therefore, it needs to be identified and managed appropriately for a better clinical outcome.

The rehabilitation management of children in the recovery phase of GBS, particularly for the cardiorespiratory endurance problem, has not been reported before. This study presents the rehabilitation assessment and treatment of a child with low cardiorespiratory endurance in the subacute phase of GBS.

CASE PRESENTATION

A 12-year-old girl was referred to the PMR outpatient clinic with a history of hospitalization due to GBS. Two months before, the patient began to feel weakness, as well as tingling sensations and numbness on both lower limbs. The weakness was slowly spreading to the upper limbs and getting worse day by day, until she was no longer able to move her legs. She also felt discomfort when breathing. At first, she got treatment at a remote hospital, but due to limited facilities, she was referred to a National Referral Hospital. The results of the cerebrospinal fluid examination correspond to the diagnosis of GBS (Table 1). Nerve conduction studies (NCS) showed signs of motor and sensory demyelination and axonal polyneuropathy, which are consistent with the acute motor sensory axonal neuropathy (AMSAN) type GBS. She received five regimens of plasmapheresis treatment, after which she felt the strength and sensibility of the extremities gradually improved for the next several days. The patient was admitted for two weeks. When she was discharged, she was able to stand up while holding on to something for less than five minutes.

Three weeks after discharge, the patient visited PMR outpatient clinic. The chief complaint at that time was easily getting tired when walking more than 100 meters. She had not returned to school yet because of the difficulty of walking for about 1 km to reach her school and climbing the stairs to reach her class room on the second floor. She also could not do her hobbies, such as playing badminton and cycling. However, she is still able to do all the self-care by herself. The patient was able to walk at a slower pace but had to stop for several minutes because of tiredness after walking 100 meters. The fatigue complaint also made it difficult for her to climb more than five stairs.

On the physical examination, there was obesity with Body Mass Index 25.7 kg/m^2. The resting heart rate was 110 times per minute, which is slightly higher than the normal value (60–100 beats per minute). The respiratory rate was 20 times per minute, which is normal for 12 year-old child. The proprioceptive and light touch functions were normal in all extremities. All the muscles strength was normal with Manual Muscle Testing (MMT) of 5, except for a slight decrease in several lower extremity muscles, such as the shoulder and hip flexor, extensor, abductor, adductor, internal rotator, and external rotator

TABLE 1
Cerebrospinal Fluid Analysis

Parameters	Results	Normal
Color	Yellowish*	No color
Turbidity	Cloudy*	Clear
Clarity	Positive*	Negative
Cells Count	127 cells/mL*	0–10 cells/mL
PMNs (segment)	8%*	0–6%
MNs (lymphocyte)	119%*	40–80%
Protein	1326 mg/dL*	15–45 mg/dL
Glucose level	136 mg/dL*	60–100 mg/dL
Chloride	109 mEq/L	115–130 mEq/L

PMNs = Polymorphonucleocytes, MNs = Mononucleocytes, *abnormal results

muscles strength (MMT 4). Her power prehension and precision grips were normal for both hands. The physiological reflexes for biceps, patellar tendon, and Achilles tendon were decreased.

Chest expansion on the axillary, xiphoid, and umbilical levels were 3, 5, and 5 cm, respectively, which are considered normal for her age. There was no accessory respiratory muscle contraction. The single breath count test (SBCT) was performed 30 times (normal cut-off value is 25 times). Standing balance, both static and dynamic, were adequate. The Borg rating of perceived exertion (RPE) at rest was 9, or "very light exertion" (on a scale of 6 to 20). We performed a six-minute walking test (6-MWT), and the distance was 150 meters, which is equal to VO2 max of 2.9 cc/kg/minute or 0.9 METs (metabolic equivalents). From the laboratory results, there was microcytic hypochromic anemia with a hemoglobin level of 9.7 g/dl. From the spirometry, FEV1 and FVC were 101% and 93%, respectively (FEV1/FVC: 110%), and were still considered normal. The peak cough flow was 360 L/minute (normal range is 147–488 liters/min for female children ages 4–18 years old). Thorax plain radiography showed no abnormality in the heart or lungs.

We prescribed a rehabilitation program that consisted of therapeutic exercise, education for increasing physical activity, and dietary management based on clinical nutritionist guidance. The hospital-based therapeutic exercises that she received were aerobic and strengthening exercises. We prescribed the exercise intensity according to the target of heart rate (HR) that was calculated with Karvonen Formula below.

Target HR = {(Maximal HR Resting HR) x Intensity %}+ Resting HR

We get the maximal HR from subtraction of 220 with the age. The exercise intensity was started at a low intensity (30–39%) for exercise adaption. Based on the formula, we got the target of heart rate of 120-140 times per minute. Aerobic exercise was performed by supervised leg ergo-cycle training for 30 minutes per session, 3 times per week. A strengthening exercise with 1 kg dumbbells was performed for the shoulder flexor, extensor, abductor, and adductor muscles, each for 3x10 repetitions. We also encouraged the patient to perform physical activity at home, which included sit to stand exercise for 3x10 repetitions and walking exercise for 30 minutes, both of which were performed 5 times per week.

At the follow-up two months later, the patient said that the tiredness when doing activities had improved. She was able to walk to school but still felt easily get tired in both legs after walking. Our physical examination showed a lower resting heart rate (91 times per minute) and a Borg RPE scale of 6. She also had increased muscle strength for the shoulder and hip muscles with MMT 5 on both sides. The 6-MWT result was 350 meters, which was equal to 4.25 METs (VO2 max 14.9 cc/kg/minute). We asked her to continue the rehabilitation program with the same types of interventions as the previous regimen. The exercise intensity was increased into moderate level. At this time, the target of heart rate was calculated with the current resting heart rate and moderate training intensity (40–60%) using Karvonen Formula, which resulted the target heart rate of 140–160 times per minute. We also encouraged the patient to start doing her previous sports activities, such as badminton and bicycling.

Two months after the last follow-up, the patient said that she no longer had complaints when carrying out her daily activities and going to school. The patient had been participating in sports activities at the school once a week. Patients routinely play bicycle three times a week for a duration of 30–60 minutes without any complaint. We performed another 6-MWT with a result of 400 meters, which was equal to 5,1 METs (VO2 max 17.8 cc/kg/minute).

DISCUSSION

Guillain-Barré Syndrome (GBS) is an autoimmune disorder manifested as myelopathy and neuropraxia.[5,6] The estimated incidence in Indonesia is 1 to 2 cases per 100,000 children, which is considered a rare case.2 It is preceded by an infection in four to six weeks before neurological symptoms emerge. The clinical manifestation of GBS is heterogeneous, with the peculiarities of progressive bilateral weakness of the limb and accompanied by the deprivation of reflexes.[7] It has several subtypes such as Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Acute Motor Axonal Neuropathy (AMAN), Acute Motor and Sensory Axonal Neuropathy (AMSAN), and Miller-Fisher Syndrome (MFS).[8,9]

The National Institute of Neurological Disorders and Stroke (NINDS) has developed diagnostic criteria for GBS.[10] In this case, the patient met the NINDS criteria for GBS. She experienced progressive bilateral sensory impairment and weakness, accompanied by decreased physiological reflexes. The CSF examination showed increased CSF protein. The NCS showed signs of motor and sensory polyneuropathy with demyelination and axonal features. Thus, she was diagnosed with AMSAN-type GBS.

GBS has been linked to spontaneous recovery that happens soon after a plateau condition is established. After a plateau, the recovery phase may last many weeks, months, or even years.[1,4,8,11] The subtype of AMSAN has an advanced, rapid clinical course. Patients often have a poor prognosis, a high death rate, and a potentially lengthy recovery time.[12] In this case, the patient received

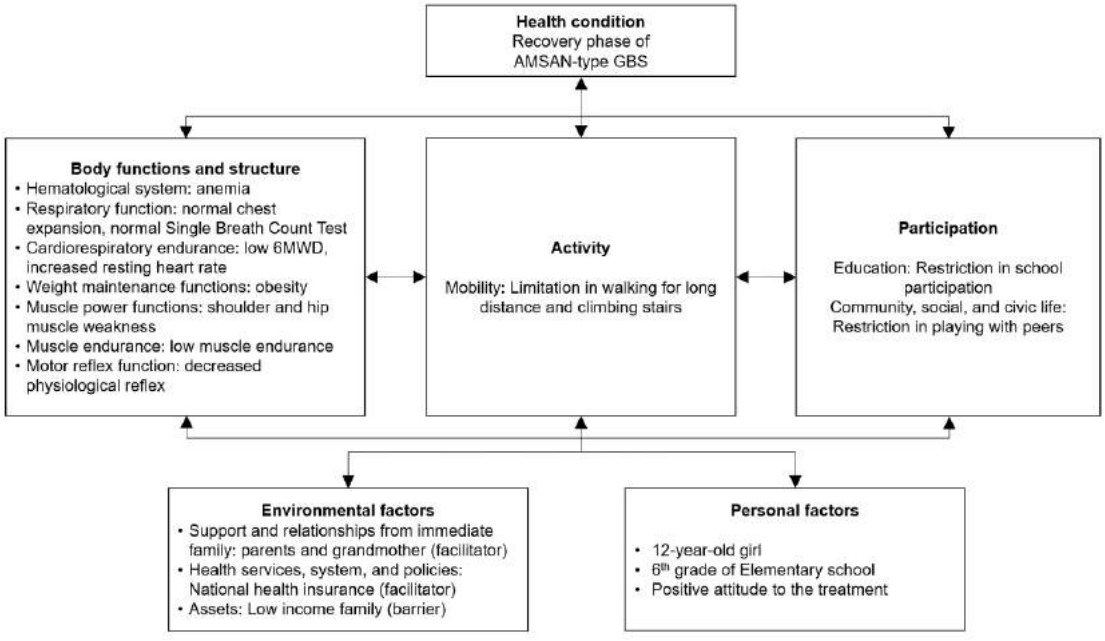

Figure 1. The International Classification of Functioning, Disability, and Health (ICF) (AMSAN = acute motor sensory axonal neuropathy, GBS = Guillain-Barré Syndrome)

five regimens of plasmapheresis treatment, which were followed by gradually improved muscle weakness. It has been demonstrated that intravenous immunoglobulin and plasma exchange are beneficial for improving illness outcomes by speeding up the recovery process. Four sessions of plasma exchange have been demonstrated to be successful; however, five sessions are more common in clinical practice.[13]

The prognosis of GBS is typically good, with 70% of patients regaining functional status, similar to the premorbid condition. However, about 20% of children have remaining disabilities after GBS.[1–3] Long-term residual complaints can include neuropathic pain, weakness, and fatigue.[1,7] The patient in this case was also complaining of tiredness at the first outpatient visit. It was the most disabling problem at that time because it limited the ability to walk more than 100 meters. It also restricted her from going to school because it was difficult for her to walk for about 1 km to reach the school and climb the stairs to her classroom.

Managing rehabilitation programs with a rehabilitation specialist and the team is a crucial step to improve the functional problems.[7,14] The goal is to optimize the activities of daily living.[7,14,15] A review study concluded that there is good evidence to support outpatient rehabilitation management in patients with GBS in the later stages of recovery to achieve long-term improvements in the levels of activity and participation.[15] The rehabilitation program in this case was arranged based on a comprehensive assessment of all the medical and non-medical factors, that can contribute to the residual disabilities.

The International Classification of Functioning, Disability, and Health (ICF) was used as a framework to describe the relationship between those factors as we can see in the Figure 1. The functional problems of this patient in terms of activity level were limitations in long-distance walking and climbing stairs. This activity limitation restricted her participation in school and playing with peers. All the functional components, including impairments in body function and structures, environmental factors, and personal factors listed on the ICF chart, can contribute to the activity and participation level.

Based on the analysis of the clinical findings, the complaint of tiredness was mainly caused by low cardiorespiratory endurance. Cardiorespiratory endurance or fitness refers to the ability of the heart and lungs to deliver oxygen to working muscles during continuous physical activity, which is an important indicator of physical health.[16–18] Good cardiorespiratory fitness causes an increase in the ability to work with higher intensity with a longer time to achieve fatigue. When the fitness level is good and the recovery is fast, it is expected that the work does not cause excessive fatigue.[18]

The gold standard for CRF evaluation is the maximum oxygen uptake (VO2max) obtained from cardiorespiratory exercise testing (CPET). In low-resource environments, submaximal and field exercise tests could be implemented to estimate the VO2max.[1,2]

Dourado The six-minute walk test (6MWT) has been validated in several populations,[9,19,20] and the distance has been proven to adequately predict the VO2max obtained in the laboratory.[21–23] In addition, this test is more representative of activities of daily living than other walking tests.[21,24] Dourado Based on the reference value chart for the six-minutes walking distance (6-MWD) in Indonesian Children, the distance that can be achieved by the patient in this case was below the 5th percentile in the initial evaluation. After the rehabilitation programs, the 6-MWD increased to be between 5th and 50th percentile.[25] We also measured the VO2max prediction and the METs level based on the 6-MWD with the VO2max prediction equation from a study.[26] The level of the METs in the initial evaluation was very low; that was not enough to perform light activities such as walking with a slow speed.[27]

A study reports the presence of significant respiratory insufficiency both clinically and qualitatively during the subacute phase of GBS.[28,29] The weakness of inspiratory and expiratory muscles in GBS can lead to poor lung compliance. This can also be compounded by immobilization; intensive unit stays, and mechanical ventilation. A single breath count test (SCBT) is a simple clinical parameter to monitor lung function.[28–30] Chest expansion has been found to be an easily measurable variable that is statistically related to restrictive abnormalities on spirometry.[28,29] However, in this case, the SCBT[30] and chest expansion[31] results were still within the normal limit. It was supported by the normal spirometry test. Thus, the respiratory impairment in this patient may not be the main factor in the low cardiorespiratory endurance. It may be more related to muscle weakness, anemia, and immobilization.

Rehabilitation programs for GBS patients should aim to restore motor function and physical condition as optimally as possible to pre-disease conditions.[14] Early rehabilitation interventions for patients with GBS, including exercise programs, have been shown to decrease chronic fatigue symptoms, improve physical fitness, walking ability, and independence in activities of daily living. As the patient got improved in sitting and standing ability, the exercise prescription focused on regaining muscular strength through aerobic exercise, resistive exercise, and the practice of functional activities. However, the intensity of exercise must be closely monitored as overwork can cause fatigue and possibly slow progress.[1,14] In addition, heart rate response to exercise in anemic children was reported less than the healthy children, because of the decrease of cardiac reserve.[32] A graded, supervised exercise program has been shown to be useful in increasing endurance.[14] In physical conditioning patients, low-intensity aerobic activity can be secure, and evidence suggests that walking and cycling may have clinically significant advantages.[1,13,14] In this case, the patient received aerobic exercise, which was gradually increased from mild to moderate intensity according to the improvement of the patient's cardiorespiratory endurance level based on the 6MWT result. The patient also received upper and lower extremity strengthening exercises to increase muscle strength. Sit to stand training was also done as a daily exercise at home. It aims to establish coordination of movements between the trunk and lower limbs and improve lower extremity muscle strength.[8]

After the rehabilitation programs, the improvement of the patient's functional condition can be observed as the level of cardiorespiratory endurance increases. Increased cardiorespiratory endurance means the increase of the ability of the heart, lung, and blood vessels to more efficiently supply the metabolic demand both at rest and during activities.[18] This can be seen from the decline in resting heart rate and RPE scale on the follow-up evaluation. At the initial evaluation, the endurance level was 0,8 METs, which was increased to 4,25 METs after two months and then 5,1 METs after three months of rehabilitation programs. Based on the METs compendium in pediatric patients, the METs level between 3 and 6 was enough to perform walking either at normal or brisk walking speed and climbing up three staircases. At the last follow-up, the patient can return to school participation and leisure activities as pre-disease condition.

CONCLUSION

Rehabilitation management, consisting of comprehensive assessments and interventions, could help children in the recovery phase of GBS to increase the cardiorespiratory endurance and regain their activity and participation.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 119–124

OPEN ACCESS

Case Report

Follicular Ameloblastoma of Maxillary: A Case Report

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1048

Accepted: December 19th, 2023
Approved: March 22th, 2024

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Abstract

Background : Ameloblastoma is a benign odontogenic tumor that appears in the mandible and maxilla. Ameloblastoma has slow growth that takes several years for symptoms to appear, but ameloblastoma in the maxilla has a more aggressive clinical course compared to the mandible. The lack of initial symptoms leading to diagnosis at an advanced disease when the tumour has already extended beyond maxilla. The cancellous structure of the maxillary bone makes it easier for tumors to spread to the nasal cavity, paranasal sinuses, orbitals, parapharyngeal tissue and skull base. This article reports a case of resection of maxillary ameloblastoma.
Case Report : A 63 year old female patient came with complaints of a lump on her right cheek since 2 years back that gradually increased in size. Since 2 months ago, pus and blood have been coming out of the lump. Extra oral examination revealed a well-defined mass with a solid and hard consistency, there were no ulcers or fistulas. Intraorally, a mass measuring 5x5x3cm was found in the region of teeth 12 to 15 which extended to the buccal-palatal area. History of allergies and weight loss was denied. Supporting examinations including panoramic radiography, PA chest radiography, CT-Scan, FNAB, and biopsy resulted in a diagnosis of ameloblastoma. Treatment was carried out by resection of the right maxillary tumor mass under general anesthesia.
Discussion : In this case, the patient's clinical examination showed a hard and large palpable swelling in the right maxilla area which extended from the region of tooth 12 to tooth 15 which caused facial asymmetry and no tooth mobility was found. This hard and painless swelling takes about 2 years before the patient experiences symptoms of pus and blood discharge. The post-maxillectomy defect in this case was covered with an intraoral prosthesis in the form of a post-surgical obturator made of acrylic resin. The obturator functions to hold the surgical packing, and prevent food or dirt contamination in the defect area which can cause infection and slow healing. The use of a prosthesis also helps restore swallowing and speech function to the patient.
Conclusion : In principle, the treatment for ameloblastoma is resection of the involved bone, as in this case the action taken is a maxillectomy. Maxillectomy can result in facial and oral cavity deformities characterised by facial disfigurement and alterations in oral functionality.Therefore, maxillary reconstruction is needed to treat maxillary defects after surgical procedures involving the loss of part or all of the maxilla.

Keywords : maxillectomy, ameloblastoma, maxillary tumor, resection

INTRODUCTION

Ameloblastoma is a benign odontogenic tumor that appears in the mandible and maxilla. This tumor is often found at the age of 30–60 years with a male to female ratio of 1:1. The clinical appearance of ameloblastoma is characterized by a lump that is painless and slow in enlargement. Pain is not a common symptom of ameloblastoma, but can occur due to bleeding in or around the tumor. Other symptoms of ameloblastoma include malocclusion, facial deformity, soft tissue invasion, or loose teeth. About 80% of ameloblastoma cases occur in the mandible, usually in the posterior area of the mandible. Maxillary ameloblastoma usually occurs in the posterior molar region. Unerupted third molars may be associated with ameloblastoma.[1–3]

The clinical progression of maxillary ameloblastoma is more severe compared to that of the mandible. This phenomenon arises as a result of the absence of initial symptoms, leading to the diagnosis being made at a late stage when the tumour has metastasized to the maxilla. The difference in bone structure between the maxilla and the mandible also influences the aggressiveness of the tumor. The bone structure of the mandible is compact, while the maxilla consists of cancellous bone, so that tumors more easily invade and spread to the nasal cavity, paranasal sinuses, orbit, parapharyngeal tissue and skull base. When symptoms begin to appear, facial deformity is often visible, usually unilateral, intraoral ulceration, toothache, headache, nasal obstruction, nasal epistaxis, and visual disturbances.[2]

CASE REPORT

A 63 year old female patient came with complaints of a lump on her upper right cheek. It was felt that the lump had appeared since 2 years ago and was small in size and was getting bigger over time. In April, the patient came to the dental and oral clinic at KRMT Wongsonegoro Hospital, Semarang, because there was pus and blood coming out of the lump, there was no decrease in appetite or weight loss. Then, supporting examinations are carried out, including dental panoramic, CT scan of the head, chest X-ray, FNAB, and biopsy of the lump. Denied history of allergies and weight loss. Biopsy results on the tissue showed that there was ameloblastoma in the right upper jaw, until finally in June 2023 the patient was referred to the Oral Surgery Polyclinic at Dr. Kariadi General Hospital Semarang Center for further treatment.

Extra oral examination (Figure 1) revealed facial asymmetry with a lump in the right maxilla, diffuse borders, the same color as the surrounding tissue, no visible edema in the right maxilla region, and no fistulas or ulcers. Palpation examination revealed a mass in the right maxillary region, firm boundaries with a firm, firm consistency, palpable paresthesia, and no palpable tenderness. Intraoral examination found a lump from the region of tooth 12 extending to tooth 15 with a size of 5 x 3 x 3 cm, with a rubbery consistency in the posterior, clearly defined, the same color as the surrounding tissue, visible buccal-palatal expansion, flat surface and visible bite marks superior to the mass, there were no ulcers or fistulas, no loose teeth were felt, and there was no tenderness.

Figure 1. Extra Oral and Intraoral Clinical Examination Before Surgery

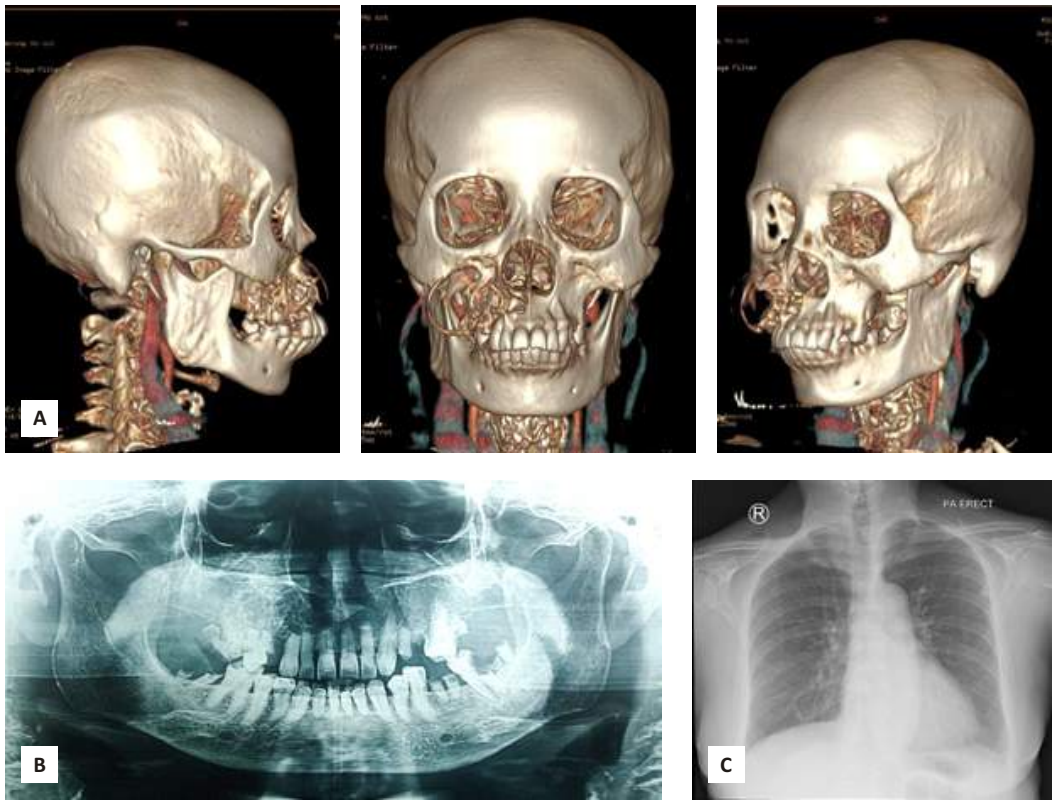

Figure 2. a. Radiographic CT scan of the head to assess the extent of the mass; b. Dental Panoramic Photo; c. Chest X-ray.

Based on the results of supporting examinations, in Figure 2a, the CT scan radiograph of the head shows a lytic lesion on the right maxillary bone – right alveolar process, geographic type 1A, multiloculated forming a soap bubble image, narrow transition zone. Multiple lymphadenopathy in the dextra colli region level 2 and left colli region levels 1,2,5 (largest size 1 x 0.8 cm, at level 5 left), no visible infarction or bleeding. The dental panoramic in Figure 2b shows a solid mass in the right maxilla which extends from the region of tooth 12 to tooth 15. The chest X-ray in Figure 2c shows cardiomegaly (LV), the pulmonary does not show infiltrates or nodules, and there is suspected left pleural effusion. Diagnosis is made using the results of an incisional biopsy, namely ameloblastoma. The lesion has a benign, locally invasive histopathology type.

After evaluating all the examinations that had been carried out, the patient underwent resection of the tumor mass in the right maxilla using a mallet and chisel (Figure 3b), and continued with adaptation of the obturator and application of gentamycin gauze to the post-mass removal defect (Figure 3c, d). The mass was removed and the obturator was placed in the defect (Figure 3e).

Evaluation at 8 days and 3 months after maxillectomy surgery, the patient came in good general condition. Extra oral examination revealed asymmetry and surgical defects. The intraoral condition is healing well, the tissue has closed and there are no signs of infection. Treatment continues by referring the patient to a prosthodontist specialist for creation of a definitive obturator. The patient's preprosthetic care included plaque control and removal of residual roots.

DISCUSSION

Ameloblastoma, also known as a benign tumour or odontogenic epithelial tumour, develops from enamel-forming tissue, which is a type of tissue that does not differentiate during the process of tooth formation.[4] Some frequently encountered characters have slow growth and may take years before symptoms develop. Often patients present with a history of painless jaw swelling, and sometimes without tooth mobility.[5] In this case, the patient's clinical examination showed a hard and large swelling in the right maxilla area which extended from the region of tooth 12 to tooth 15 which caused facial asymmetry and no tooth mobility was found. This hard and painless swelling takes about 2 years before the patient experiences symptoms of pus and blood discharge.

In principle, the treatment for ameloblastoma is resection of the involved bone, as in this case the action taken is a maxillectomy. Maxillectomy is the surgical

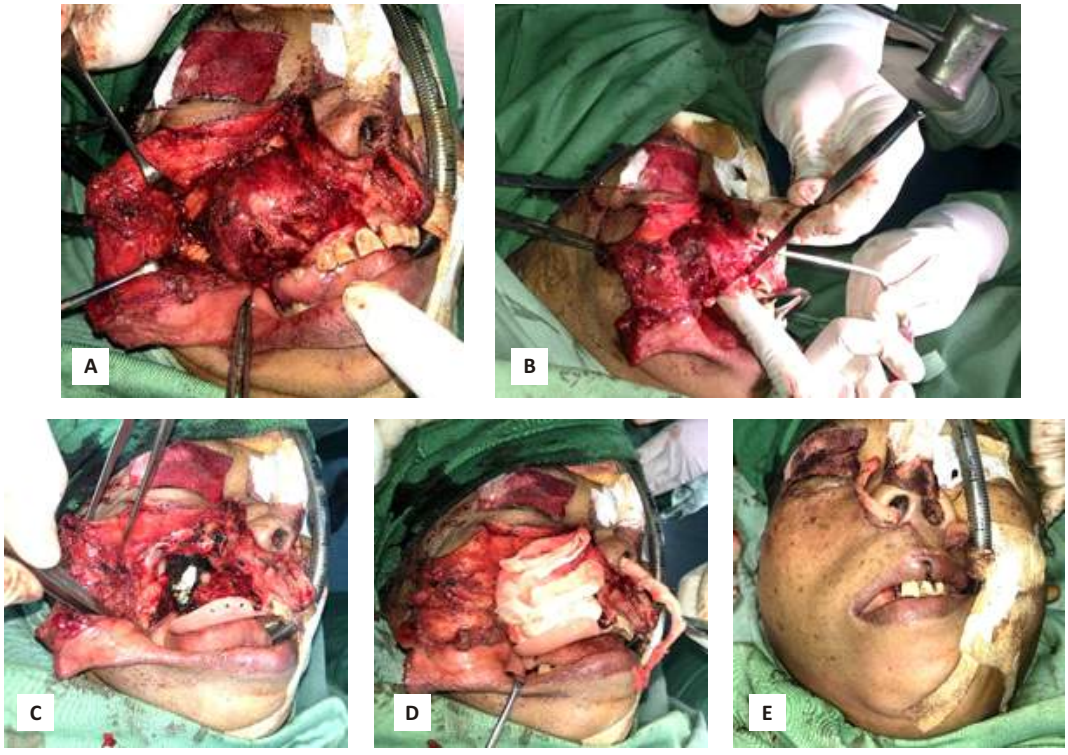

Figure 3. a. Durante OP Clinical Photos: a, b. Dextra maxillectomy; c, d. Adaptation of the surgical obturator to the defect and application of gentamicin gauze to the defect post mass removal, and; e. Post surgery.

Figure 4**.** Extra oral and intraoral clinical examination 8 days after surgery

Figure 5. Extra oral and intraoral clinical examination 3 months after surgery

removal of the maxilla, often called maxillary resection.[6] Maxillectomy can cause defects in the face and oral cavity in the form of damage and changes in facial shape and oral function. Maxillary reconstruction is rehabilitation treatment for maxillary defects after surgical procedures involving the loss of part or all of the maxilla.[7,8]

Research by Petrovic (2018) Resection maxillary ameloblastoma should achieve negative margin using partial, total or extended maxillectomy depending on the extent of the tumor. Clear margins obtained with adequate resection of the soft tissure surrounding the tumor. Cupping or indentation of alveolar bone need excision of associated periosteum and/or bone. Studies shown that inadequate initial surgical treatment of ameloblastoma leading to high risk of local recurrence with rates of 16 to 19%. However, only 80% of recurrent ameloblastoma are cured with another resection.[9]

Reconstruction of the post-maxillectomy defect in this case used a surgical phase obturator prosthesis. The obturator is made before the maxillectomy operation with an acrylic base and a clamp wire on the remaining teeth. Obturator fixation is carried out by suturing the mucosal tissue to the obturator which has previously been perforated along the side of the prosthesis. The obturator functions to hold the surgical packing, and prevent food or dirt contamination in the defect area which can cause infection and slow healing. The use of a prosthesis also helps restore swallowing and speech function to the patient.[10]

Surgical packing of the defect area uses gauze that has been given gentamicin and is arranged to fill the defect cavity with the end of the gauze coming out of the nostril. The aim of giving gauze is to absorb bleeding, thereby preventing blood-filled dead space which can become a focal infection. The gauze was removed on day 5 after resection under general anesthesia. Soft tissue healing usually occurs around 3–5 days after resection.[10]

Reconstruction of post-maxillectomy defects must be carried out considering that if left unchecked it will result in high morbidity, namely, severe disturbances in function (swallowing, speaking) and cosmetics.[7] The aim of reconstruction of maxillary defects is to maintain the food passage (maintain alimentation), maintain the form of speech (restore speech), maintain the shape of the cheeks and lips (provide lip and cheek support) and maintain the shape of the face (re-establish midface projection).[8]

Post-maxillectomy management includes installing an obturator and administering adequate medication.[8] After maxillectomy, the patient was given systemic medication in the form of a combination injection of amoxicillin 1000mg and clavulanic acid 200mg (1200mg/12 hours), Metronidazole inf 500 mg/100 ml (500mg/8 hours), Ketorolac inj 30mg/ml (30mg/12 hours), ranitidine inj 50mg/2ml (50mg/ 12 hours) for 5 days. The patient was discharged on the 5th day after surgery with outpatient medication in the form of Amoxicillin tab 500mg (500mg/8 hours),

Diclofenac Sodium enteric tab 50mg (50mg/8 hours), and Dexamethasone tab 0.5mg (0.5 mg/8 hours) for 5 days, accompanied by topical treatment using 0.3% Gentamycin ointment (topical/12 hours).

Control 3 months after maxillectomy the patient came in good general condition. Extraoral inspection revealed good soft tissue healing. Intraoral examination shows that primary healing has occurred where the defect has closed completely. There are no signs of inflammation or infection. The next treatment is to make a definitive prosthesis, namely a removable denture. Dentures are needed to restore aesthetic function, speech function, swallowing and mastication in patients so that they can improve the patient's quality of life after maxillectomy.

CONCLUSION

In principle, the treatment for ameloblastoma is resection of the involved bone, as in this case the action taken is a maxillectomy. Maxillectomy can cause defects in the face and oral cavity in the form of damage and changes in the shape of the face and oral function. Therefore, maxillary reconstruction is needed to treat maxillary defects after surgical procedures involving the loss of part or all of the maxilla.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; vol 11 (1) : 125–131

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Case Report

Case Series : Orbital Complications in Pediatric Rhinosinusitis

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v11i1.1073

Accepted: January 09th, 2024
Approved: March 25th, 2024

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Abstract

Background : Acute bacterial rhinosinusitis in children can cause orbital complications, either directly through fissures or indirectly through veins. Proper treatment can reduce morbidity due to orbital complications.
Case : Two cases of orbital complications in pediatric acute bacterial rhinosinusitis caused by adenoid hypertrophy and dental infection. The first case of acute bacterial rhinosinusitis with periorbital cellulitis and left premaxillary abscess accompanied by adenoid hypertrophy and multiple pulp gangrene. The second case of acute bacterial rhinosinusitis with subperiosteal abscess accompanied by adenoid hypertrophy and multiple dental caries. Functional endoscopic sinus surgery (FESS), abscess drainage, adenoidectomy and odontectomy were performed. The culture results of the first patient were *Streptococcus anginosus*, and it was resistant to tetracycline. Meanwhile, the culture results of the second patient, *Staphylococcus epidermidis*, were resistant to amoxiclav, ampicillin, cefoxitin, oxacillin, penicillin G, and tetracyclin.
Conclusion : Acute rhinosinusitis with orbital complications can caused by adenoid hypertrophy and dental infection. Medical treatment with adequate antibiotic followed by FESS, abscess drainage, adenoidectomy and odontectomy give an optimal result.

Keywords : pediatric rhinosinusitis, acute bacterial rhinosinusitis, orbital complication, odontogenic, adenoid hypertrophy

INTRODUCTION

Rhinosinusitis is a significant health problem affecting 5–28% of the general population and up to 2–4% of children. Children have unique risk factors for rhinosinusitis when compared to adults, the paranasal sinuses in children are smaller and are undergoing the process of maturation and development, so they are at higher risk of obstruction. Obstruction of the sinus ostium and osteomeatal complex may be facilitated by the presence of allergic and inflammatory factors, upper respiratory tract infections, and adenoid hypertrophy, which are common conditions in childhood. The prevalence of adenoid hypertrophy is 34% in pediatrics, being the most common cause of nasal obstruction in childhood.[1]

The impact of rhinosinusitis on a child's quality of life is greater than that of other diseases such as asthma, attention deficit hyperactivity disorder (ADHD), juvenile rheumatoid arthritis, and epilepsy.[2] Purulent rhinosinusitis involving the frontal and ethmoid sinuses can cause orbital complications due to spread of infection through the thin lamina papyracea, thrombophlebitis, or through venous drainage.[3,4] Rhinosinusitis causes 66 – 82% of orbital infections, and acute ethmoiditis is the rhinosinusitis most associated with orbital cellulitis, especially in children.[5]

The prognosis of pediatric patients with chronic rhinosinusitis depends on the degree of severity, complications that have occurred, and is influenced by host factors, the environment, and the patient's compliance with treatment. Complications increase patient morbidity and mortality. Pharmacological therapy for chronic rhinosinusitis in children has a success rate of approximately 50%.[2] With the implementation of surgical therapy, the patient's prognosis improves.[6,7]

This article presents 2 cases of orbital complications in pediatric rhinosinusitis with the aim of determining the appropriate diagnosis and management of cases of rhinosinusitis in children with orbital complications thereby reducing morbidity and mortality rates.

CASE

The first patient, a 13-year-old child, was referred with a swollen and painful left eye for 5 days, accompanied by blurred vision, difficulty opening the eyelids, watery eyes and yellowish discharge from the eyes. 2 weeks previously the patient complained of pain in the upper left tooth, then swelling and pain in the left cheek. The results of the physical examination showed edema in the left premaxilla to the inferior palpebra of the left eye, accompanied by hyperemia, tenderness and mucopurulent discharge in the medial canthus. Left eyeball movement and vision were within normal limits. Nasal endoscopy revealed edema of the inferior turbinate, mucopurulent discharge and the lateral wall of the left nasal cavity was pushed medially causing the middle meatus to be closed. Hypertrophic adenoids were seen accompanied by mucopurulent discharge in the nasopharynx.

The results of a CT scan of the paranasal sinuses showed isodense lesions in the left maxillary, ethmoid, frontal and sphenoid sinuses, accompanied by isodense images in the premaxilla to the left inferior eyelid, and no destruction of the lamina papyracea was seen. The patient was diagnosed with acute rhinosinusitis complicated by premaxillary abscess and odontogenic preseptal cellulitis. The diagnosis by the oral surgeon was pulp necrosis 2.4, 5.5, 5.3, 6.5, 7.5. This patient received ampicillin sulbactam and metronidazole intravenous. An endoscopic sinus surgery and adenoidectomy was performed by an ENT doctor followed by an odontectomy and abscess incision by an oral surgeon. During surgery, polyps and mucopurulent discharge were found in the maxillary sinus, ethmoid and left frontal recess. Meanwhile, in the sphenoid sinus, edematous mucosa and mucoid discharge were found. Pus was found in the bucogingival sulcus in the left 2.3 – 2.6 tooth region.

Postoperative evaluation of the left premaxillary region is not edematous and not hyperemic, the left inferior palpebra is slightly edematous but not hyperemic. The results of surgical tissue culture showed *Streptococcus anginosus*, and was resistant to tetracycline.

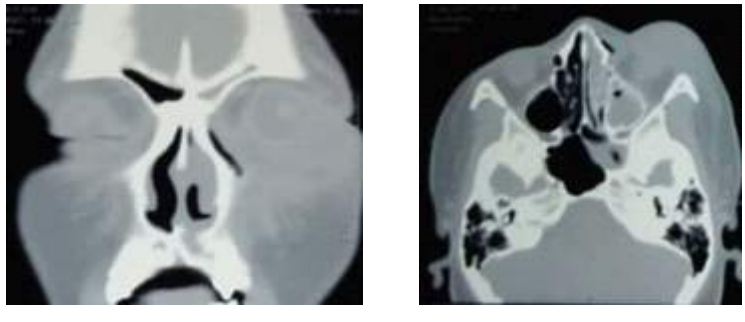

Figure 1. CT scan of the paranasal sinuses A. Coronal section B. Axial section

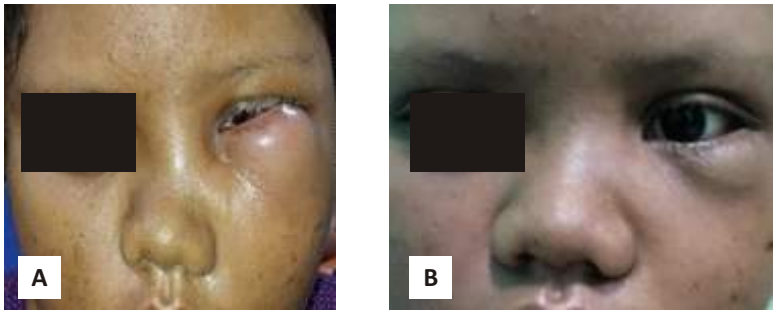

Figure 2. A. Patient profile before surgery. B. Patient profile 3 days after surgery.

Figure 3. CT scan of the paranasal sinuses A. Coronal section B. Axial section

Patient had cefixime tablet for home treatment.

The second patient, an 8-year-old child was consulted by an ophthalmologist with left eye swelling, pain and redness for 2 weeks. The results of the physical examination revealed lagophthalmos in the left eye, edema in the superior palpebra, accompanied by hyperemia, tenderness, and mucopurulent discharge. Movement of the eyeballs is hampered in all directions accompanied by pain and visual acuity in the left eye is 6/48. Nasal endoscopy revealed edema, hyperemia and mucopurulent discharge in the middle meatus. Hypertrophic adenoids were seen accompanied by mucopurulent discharge in the nasopharynx.

The results of the MSCT scan revealed an inhomogeneous lesion in the extraconal left orbital cavity (measure ± AP 3.7 x LL 2.1 CC 2.6 cm) which was pressing on the medial rectus muscle, optic nerve and bulbus oculi to the left antero-infero-lateral. The lesion extended to the anterior ethmoid sinus and maxillary sinus, accompanied by destruction of the left lamina papyracea. Dental examination showed carious and loose teeth 5.2, 5.4, 6.2, 6.4, 6.5, 7.1, 7.4, 7.5, 8.1, 8.4, and 8.5

The patient was diagnosed with acute rhinosinusitis complicated by subperiosteal abscess. This patient initially received ampicillin sulbactam and metronidazole therapy, but was later replaced with ceftriaxone because there was no significant improvement. Endoscopic sinus surgery was performed with orbital decompression and adenoidectomy by an ENT doctor and incision of the abscess by an ophthalmologist. During surgery, polyps and mucopurulent discharge were found in the maxillary sinus, ethmoid and left frontal recess. There was a defect in the left lamina papyracea, orbital decompression was performed and purulent discharge was found from the left medial orbit. The action was continued by the oral surgeon to eradicate the focal infection.

Postoperative evaluation showed that the eyelids were slightly edematous but not hyperemic. The results of surgical tissue culture showed that *Staphylococcus epidermidis* was resistant to amoxiclav, ampicillin, cefoxitin, oxacillin, penicillin G, and tetracycline. Patient had ciprofloxacin tablet for home treatment.

DISCUSSION

Rhinosinusitis in children according to EPOS is defined as the presence of two or more symptoms, one of which must be nasal congestion/obstruction/congestion or nasal discharge (anterior or posterior), which may be accompanied by pain/pressure on the face or coughing. This needs to be supported by the results of a nasal endoscopic examination, or relevant changes in a computed tomography (CT) scan of the sinuses.[2] To distinguish between acute and chronic rhinosinusitis, it is judged by the onset of symptoms, with a cut-off of

Figure 4. A. Patient profile before surgery. B. Patient profile 3 days after surgery.

TABLE 1
Orbital complications based on Chandler classification.[13]

Classification	Description	Signs and symptoms
Periorbital cellulitis	Inflammation and edema of the anterior orbital septum	Eyelid edema Inhibition of eye movement (-) Vision loss (-)
Orbital cellulitis	Extension of inflammation and edema beyond the orbital septum	Diffuse edema in the orbital contents Inhibition of eye movement (+) Vision loss (+)
Subperiosteal abscess	Collection of pus in the lamina papyracea, periorbital and orbital bone walls	Eyeballs are destroyed/squeezed
Orbital abscess	Purulent collections occur within the orbital	Proptosis (+) Chemosis (+) Ophthalmoplegia (+) Vision loss (+)
Cavernous sinus thrombosis	On both eyes. Caused by the extension of infection to the posterior side through the superior ophthalmic vein and cranial nerves.	Cavernous sinus thrombosis, meningitis, subdural empyema, and brain abscess can develop if not treated appropriately.

12 weeks. It is said to be acute if the onset is less than 12 weeks and chronic if 12 weeks or more.[2]

In this case report, acute rhinosinusitis was found in both patients, characterized by complaints of one-sided nasal congestion, runny nose with thick mucus and cough with an onset of less than 12 weeks. Only the first patient complained of facial pain, namely the left cheek, VAS 6, due to swelling of the gums, cheek and left eye. On endoscopic examination, the mucosa was edematous, hyperemic and purulent discharge in the middle meatus of both patients and the CT-scan image showed mucosal changes in the unilateral paranasal sinuses which supported the diagnosis of acute rhinosinusitis in this case.

The pathogenesis of rhinosinusitis arises from changes in the homeostasis of sinus and nasal drainage, which under normal conditions is guaranteed by the patency of the sinus ostium, adequate and active mucus production, and effective ciliary function. However, children have unique risk factors for rhinosinusitis when compared to adults. In children, the paranasal sinuses and ostia are smaller and are undergoing the process of maturation and development, so they are at higher risk of obstruction. Obstruction of the sinus ostium and osteomeatal complex is supported by the presence of allergic and inflammatory factors, upper respiratory tract infections, and hypertrophic adenoids, which are common conditions in childhood.[1]

The risk factors found in both cases were adenoid hypertrophy and dental caries. The prevalence of adenoid hypertrophy is 34% in pediatric settings and is the most common cause of nasal obstruction in childhood. Adenoid hypertrophy causes inflammation in the nasopharynx, nasal cavity and can cause rhinosinusitis. When the osteomeatal complex is obstructed due to mucosal edema, negative pressure and hypoxia develop in the sinuses, stimulating the production of mucus and favoring its retention, leading to bacterial growth and the onset of acute rhinosinusitis.[1]

Odontogenic rhinosinusitis is an inflammatory

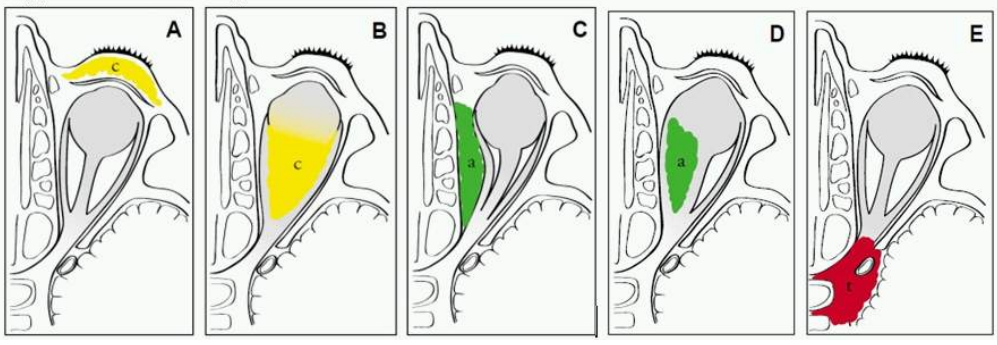

Figure 5. Classification of sinusitis with orbital complications:
A. Periorbital cellulitis, B. Orbital cellulitis, C. Periorbital abscess, D. Orbital abscess, E. Cavernous sinus thrombosis.[14]

TABLE 2
Comparison of eye examination and CT scan

Variable	Case 1	Case 2
Signs and symptoms	Swollen eyes	Swollen eyes, eye movement disorders
Physical examination	Edematous inferior eyelids, hyperemic, purulent discharge, eye movements and visual acuity are within normal limits	Lagophthalmus, edema and hyperemia of the palpebra, obstructed eye movement, decreased vision
CT scan (sinus paranasal)	Isodense lesions in the left maxillary, ethmoid, frontal and sphenoid sinuses, accompanied by inhomogeneous lesions in the premaxilla to the left inferior eyelid, no visible destruction of the lamina papyracea.	Inhomogeneous lesion in the extraconal left orbital cavity that pushes the medial r ectus muscle, optic nerve and bulbus oculi to the left antero-infero-lateral. Isodense lesions of the anterior ethmoid sinus and maxillary sinus, accompanied by destruction of the lamina papyracea.

condition in the paranasal sinuses which is the result of dental pathology based on the results of clinical, radiographic and/microbiological examinations.[8] Approximately 10% of all sinusitis cases are the result of an odontogenic process. Secondary odontogenic rhinosinusitis accounts for 10–14% of total maxillary sinusitis. Of the total cases of unilateral maxillary sinusitis, odontogenic causes account for approximately 75% of cases.[9]

Odontogenic infections begin with the attachment of bacteria to the outer surface of the tooth, eventually destroying the outer enamel and inner dentin and entering the vital pulp. Once the infection enters the pulp, it causes necrosis and pus formation. Bacteria invade the apical part of the root and cause periapical infection. Bacteria from the lesion can spread to adjacent tissues and activate a reaction from the Schneiderian membrane epithelium. Extrusion of dental material used in root canal therapy into the maxillary sinus also has a high risk of CRS.[8] Maxillary dental caries was found in both patients, which could become a focal infection resulting in unilateral rhinosinusitis.

The spread of odontogenic infections to the orbit can be through various routes, including: 1) inferior orbital fissure or previously formed gap in the floor of the orbit, 2) canine fossa, spreading to the periorbital tissue directly, 3) premaxillary fascia above the thin buccal cortical plane which can be easily eroded, 4) the infratemporal fossa or pterygopalatine fossa and reaches the orbit through the infraorbital fissure, 5) The medial orbital wall or lamina papyracea which has natural dehiscence and thin neurovascular perforations can be easily damaged due to sinus infection, 6) another route is through Facial thrombophlebitis, which includes retrograde spread of the ocular veins.[2,9-11] In the first case, a premaxillary abscess was found in the region of teeth 2.3 – 2.6, so the possible route of infection to the orbit was through the premaxillary fascia, canine fossa and inferior orbital fissure. In the second case, there was maxillary sinusitis, ethmoiditis and destruction of the lamina papyracea so that the possible route of infection to the orbit was through the inferior orbital fissure and lamina papyracea defects in the ethmoidal sinus.

Several prospective studies place the incidence of

orbital abscess at 1.6/100,000 in children and 0.1/100,000 in adults.[12] More than 70% of orbital infections develop as complications of paranasal sinusitis, while the remaining 30% originate from the eyelids, tonsils, intracranial areas, middle ear, and odontogenic structures.[2] The orbits are affected in 85% of acute sinusitis with complications.[13] The classification of orbital complications according to Chandler consists of periorbital cellulitis, orbital cellulitis, periorbital abscess (subperiosteal abscess), orbital abscess, and cavernous sinus thrombosis.[14,15]

Orbital complications based on Chandler's criteria in the first case correspond to the description of preseptal cellulitis while the second case corresponds to the description of subperiosteal abscess (Table 2).

The principle of management of rhinosinusitis with orbital complications is to eradicate infection and inflammation of the sinus by opening the ostium, restoring drainage and ventilation of the sinus, and providing access for drainage of orbital abscess. Therapy is given according to etiology, classification of rhinosinusitis and classification of orbital complications according to Chandler. Antibiotics are the therapy of choice in acute bacterial rhinosinusitis, given for 10–14 days even if the clinical symptoms have disappeared. The antibiotic chosen is a broad spectrum, namely the penicillin group such as amoxicillin. If there is antibiotic resistance, amoxicillin-clavulanate or 2nd generation cephalosporin can be given. The initial antibiotic for both of our patient was ampicillin sulbactam and metronidazole, and it give good result for first patient. The second patients change to ceftriaxone because there was no improvement, and this is relate with the sensitivity result which is show resistance to amoxiclav, ampicillin, and penicillin G. Sinus culture is very important in determining which antibiotic to use.[1] Other symptomatic therapies that can be given include analgesics, mucolytics (oral or topical steroid guaifenesin), irrigation/nasal wash with NaCl.[2,16] The first and second patients were found to be resistant to tetracycline, the second patient was also resistant to the penicillin group, including amoxicillin and amoxicillin clavulanate. Both patients received ampicillin sulbactam before the culture and sensitivity results were available. After surgery, the second patient's antibiotic was changed to ciprofloxacin according to the antibiotic sensitivity results and because patient resistant to amoxiclav, ampicillin, and penicillin G.

Management of orbital complications depends on the stage of the Chandler classification. Most cases of periorbital cellulitis and orbital cellulitis can be treated effectively with intravenous antibiotics. Indications for surgery in cases with stage I or II orbital complications if the patient's condition worsens within 24–48 hours after administration of antibiotics, decreased visual function, increased levels of proptosis and ophthalmoplegia, and there is an abscess on radiological examination with CT scan.[17] Both patients underwent functional endoscopic sinus surgery (FESS) according to the presence of visible sinuses, adenoidectomy and odontectomy to eradicate the focal infection. The indication for surgery in the first patient was no clinical improvement and CT scan results of the paranasal sinuses after intravenous antibiotic administration. Meanwhile, in the second patient, the indication for surgery was due to the presence of a subperiosteal abscess.

The second patient underwent orbital decompression to drain the sub-periosteal abscess. Treatment of subperiosteal abscesses must be done immediately, namely drainage of the abscess with orbital decompression. Orbital decompression can be performed via lateral canthotomy, inferior cantholysis or incision of the periorbital periosteum after removal of the lamina papyracea.[17] According to Froenhlich *et al*, as quoted by Sciaretta *et al*, treating periorbital abscesses with endoscopy by performing anterior ethmoidectomy and opening the anterior part of the lamina papyracea is adequate for drainage of the abscess. Orbital decompression with endoscopic sinus surgery is an option for treating periorbital abscess.[17]

According to Pat and Manning, orbital and sinus surgery in cases of orbital abscess is carried out if clinically and radiologically there are signs of suppuration, decreased visual acuity in immunocompromised patients, more serious complications such as blindness and afferent pupillary defects with ipsilateral cellulitis, and the presence of progression in the orbit despite administration of intravenous antibiotics. Clinical and radiological examination showed signs of suppurative inflammation so that incision and drainage were necessary. This procedure is to prevent further complications such as septicemia and pneumonia.[17]

CONCLUSION

Pediatric acute rhinosinusitis with orbital complications can cause by adenoid hypertrophy and dental infection. Morbidity can be prevented by administering adequate antibiotics according to culture and sensitivity testing accompanied by surgery. The surgical management consist of FESS, abscess drainage, adenoidectomy and odontectomy give an optimal result and reduce the possibility of recurrency.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; Vol 11 (1)
March 2024

AUTHOR GUIDELINE

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3. Consists of 3-8 keywords
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2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
6. Explains computer program (software) used
7. Explains ethical clearance and informed consent

Results :
1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
5. Provides hypothesis without commentary

Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*) www.icjme.org

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2024; Vol 11 (1)
March 2024

Authors and institutions :

1. Present complete name of authors without academic title along with office/institution/work place address under the title
2. Provide correspondences
   The main author provides a statement explaining that article has never been published nor sent for publication to other journals and has already been approved by all co-authors evidenced by a statement sheet. All sent articles are reviewed by profession groups (peer reviewers) and editors. All articles should provide ethical clearance issued by Ethical Review Board and 2 sheets of inform consent form already signed in "pdf" format.

CASE REPORT

Title :
1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, case report, discussion, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (justification of the case report). The second paragraph consists of aim of case report emphasizing diagnose/pathogenesis/therapy.
2. Is supported by relevant and strong references

Case report :
1. Presents short case involving medical history, physical examinations, and investigations.
2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
4. Obtains patients' or families' informed consent for publication for patients with easily identified features. Editors may conceal physical features considered unnecessary.
5. Contains maximum four photos/pictures for each article.

Discussion :
1. Provides epidemiology data showing that rare cases occur or new procedures are conducted.
2. Provides relevant discussion according to aim of the case report emphasizing diagnose/pathogenesis/therapy comparing/relating to other cases and providing LoE (Level of Evidence).

Conclusion and suggestion :
1. Are in line with the aim of case report.
2. Suggestion consists of improvement for case management.

Reference :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*). www.icjme.org

Author and institution :
1. Complete name of authors and office/institution/workplace address are presented under the title.

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SERTIFIKAT

Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
Kementerian Pendidikan, Kebudayaan, Riset dan Teknologi Republik Indonesia

Kutipan dari Keputusan Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi Republik Indonesia

Nomor 105/E/KPT/2022
Peringkat Akreditasi Jurnal Ilmiah Periode 1 Tahun 2022

Nama Jurnal Ilmiah

Medica Hospitalia : Journal of Clinical Medicine

E-ISSN: 26857898

Penerbit: RSUP Dr. Kariadi Semarang

Ditetapkan Sebagai Jurnal Ilmiah

TERAKREDITASI PERINGKAT 3

Akreditasi Berlaku selama 5 (lima) Tahun, yaitu
Volume 8 Nomor 2 Tahun 2021 Sampai Volume 13 Nomor 1 Tahun 2026

Jakarta, 07 April 2022
Plt. Direktur Jenderal Pendidikan Tinggi,
Riset, dan Teknologi

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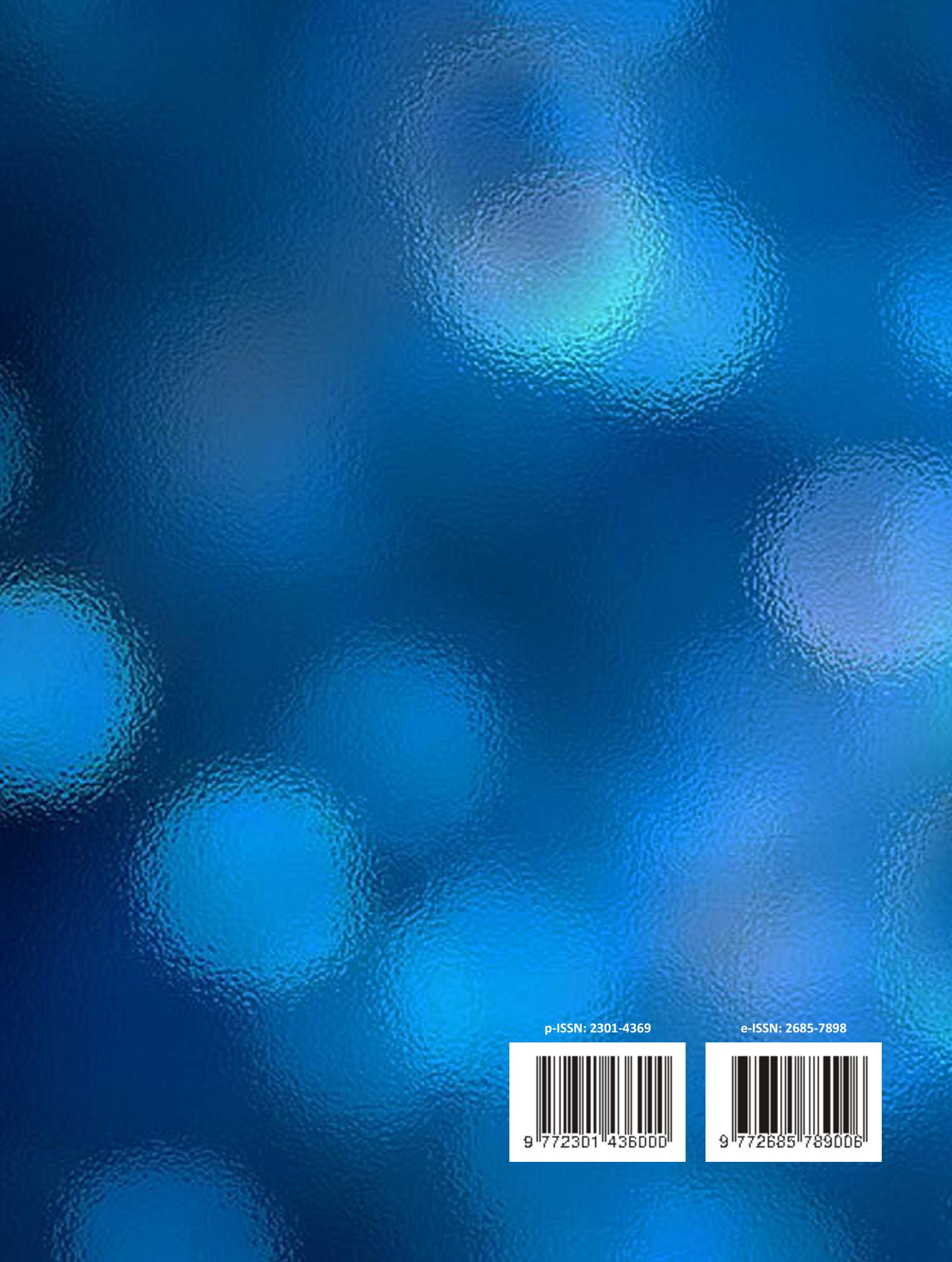

p-ISSN: 2301-4369

e-ISSN: 2685-7898