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Original Articles

Case Report

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Original Articles

167 The Relationship between Cumulative Platinum-Based Chemotherapy Dose and The Occurrence of Ototoxicity in Head and Neck Malignancies

Hendro Purnomo[1], Dwi Marliyawati[1], Zulfikar Naftali[1], Dian Ayu Ruspita[2], Muyassaroh[2]
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There was a significant association between cumulative doses of platinum-based chemotherapy and ototoxicity incidence of head and neck malignancy patients.

172 Risk Factors for Peripheral Vertigo

Yuni Retno Sekarwangi[1], Dwi Marliyawati[2], Kanti Yunika[2], Zulfikar Naftali[2]
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[2]Departement Otorhinolaryngology, Faculty of Medicine, Diponegoro University Semarang, Indonesia

The significant risk factor associated with the occurrence of peripheral vertigo was hypertension by 6.964 times.

177 The Effect of Cold Temperature on the Severity of Allergic Rhinitis Based on Visual Analog Scale (VAS) Score among Medical Students of Malikussaleh University

Farianti Zuhra[1], Mulyati Sri Rahayu[2], Baluqia Iskandar Putri[3]
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[3]Division of Otorhinolaryngology, Faculty of Medicine of Malikussaleh University, Lhokseumawe, Indonesia

The results of this study indicate that the effect of cold temperature can increase the severity of allergic rhinitis.

183 Significant Relationship between Brixia Score and The Degree of Acute Respiratory Distress Syndrome in Covid 19 Patients

Irni Dwi Aprianty Ibrahim[1], Bambang Satoto[2], Thomas Handoyo[3], Antonius Gunawan Santoso[4], Hermina Sukmaningtyas[4], Farah Hendara Ningrum[4]
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Brixia score has a significant relationship to the degree of ARDS in COVID-19 patients.

188 Correlation Between Brixia Score Imaging and Clinical Laboratory Results in Severe-Critical Covid-19 Patients Receiving Standard Therapy Compared to Tocilizumab

Aulia Fitriani[1], Frederica Mardiana Wahyuni[1], Bambang Satoto[1], Thomas Handoyo[2], Antonius Gunawan Santoso[1], Christina Hari Nawangsih[1], Nurdopo Baskoro[1]
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There is a significant correlation between the Brixia score results and the D-dimer results in COVID-19 patients who are adiministered standard therapy, but not significant correlation in tocilizumab.

193 The Effectiveness of Macrophage Hydrolyzed VCO Cream in Healing Second Degree Burns in Wistar Rats

Fahmi Syarif[1], Najatullah[2]
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[2]Department of Plastic Surgery, Faculty of Medicine, Diponegoro University / Kariadi Hospital, Semarang, Indonesia

100% hVCO is effective in accelerating second degree burn wound healing in terms of macrophage count.

198 The Increased Superoxide Dismuatase (SOD) in Mice Infected by *Plasmodium Berghei* ANKA Treated with Nanoparticle Extract of Beetroot *(Beta Vulgaris L)*

Fransisca Pramesshinta Hardimarta[1,2], Lisyani Budipradigda Suromo[3], Kis Djamiatun[4]
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Supplementation of beetroot extract nanoparticles has an antioxidant effect by increasing SOD levels in mice infected with malaria and receiving artemisinin therapy.

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Editorial

In this modern era, technology has brought revolutionary changes in various fields, including in the world of medicine. One of the leading innovations in the world of surgery is the minimally invasive surgery. It has made a major contribution for advancing medical practice by offering a safer, faster and more efficient approach to perform surgical procedures. It is important to understand that minimally invasive surgery is not the solution for all medical cases. Some cases still require conventional surgical methods for optimal results. However, along with the technological advancement, minimally invasive surgery is increasingly used and developed for various types of medical conditions.

Likewise with the advancement of radiodiagnostic technology, procedures such as tumor biopsies, blood vessel imaging, and cardiac imaging can be performed with excellent precision, reducing risk complications and accelerating healing process. In addition, radiodiagnostics plays an important role in early detection of diseases, thus providing opportunities for early treatment and increasing healing rate.

In this edition, there are studies with good principles, using advanced technology, showing many fields that can produce outputs supporting the development of science. In any discipline, there are many things around hospital that can be sources of research.

Scientific articles related to medical techniques are important means of presenting innovations in health sector. Through these articles, researchers and medical practitioners can share the latest knowledge and experiences regarding the latest medical technologies, such as minimally invasive surgery and radiodiagnostics. By compiling scientific articles, we can improve understanding and application of more cutting-edge medical techniques, thus providing great benefits to patients and medical personnel. Support for producing scientific articles needs to be continuously improved to encourage the creation of new breakthroughs and improve the quality of health services as a whole.

Editor

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Original Article

Comparison of the Effectiveness of High Intensity Laser therapy (HILT) and Low-Level Laser Therapy (LLLT) on Functional Improvement in Knee Osteoarthritis Patients

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Abstract

Background : Knee osteoarthritis causes sore, joint stilted, progressive deformity and functional encroachment. The current therapeutic focus on rectifying function and assuaging symptoms, especially pain. There are two types of laser therapy, namely Low-Level Laser Therapy (LLLT) and High Intensity Laser Therapy (HILT). High Intensity Laser Therapy (HILT) is a high-intensity laser radiation with photochemical, photothermal, and photomechanical action possess many therapeutic steads including analgesic, anti-edematous, and biostimulating effects. In this study, we compare the effectiveness of HILT with LLLT on functional enhancement in knee osteoarthritis assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS). The aims of this study was to compare the effectiveness of HILT with LLLT on functional enhancement in patients with knee osteoarthritis.
Methods : This research is a quasi-experimental pre-test and post-test with controlled group design. There were 27 subjects of knee osteoarthritis patients who were divided into 2 treatment groups, the first treatment group admit HILT therapy (14 patients) and the second treatment group admit LLLT therapy (13 patients). Knee Injury and Osteoarthritis Outcome Score (KOOS) was measured before and after 4 weeks of treatment.
Results : There was a significant difference in the mean value of functional improvement as measured by KOOS before and after treatment in each group ($p < 0.001$) and there was a significant difference in the mean value of KOOS in the two groups ($p < 0.001$).
Conclusion : The administration of HILT has shown significant escalation of functional improvement compared to the administration of LLLT in patients with knee osteoarthritis.

Keywords : Knee Osteoarthritis, Functional improvement, HILT, LLLT

INTRODUCTION

Chronic disease of the musculoskeletal system is one of the most common health jeopardy in the world's population, with osteoarthritis (OA) of the knee becoming a profound age-related public health problem. This condition is a progressive multifactorial joint disease peculiar by progressive bereavement of articular cartilage and results in pain, functional nuisance, functional disability, and degression patient quality of life.[1] Ten percent of the population over 60 years complains about this condition. In the United States, 37% of the population over 60 is diagnosed with knee osteoarthritis.[2]

The prevalence of knee OA has terrace significantly over the last decade. It is expected to continue to increase, partly because of the escalated prevalence of obesity, other risk factors and other independent causes. It is estimated that the prevalence of knee OA in adults aged 60 years and over is 10% in men and 13% in women. The results of the 2018 Basic Health Research (Riskesdas) by the Indonesian Ministry of Health, the prevalence of osteoarthritis terrace with age was 15.55% in those over 55 years of age, 18.63% in those over 65 years and 18.95% in those under over 75 years, as much as 6.1% in men and 8.5% in women.[2,3]

Treatment of knee OA is directed to rectify joint soreness and stilted, maintain and escalate joint mobility, alleviate physical disability, escalate health-related quality of life, restrain the progression of joint damage, and educate patients about the nature of disorder and its management.[4] A comprehensive plan for managing OA in patients can appertain educational, behavioral, psychosocial, and physical interventions, topical, oral, and intra-articular medications, physical modalities, and exercise therapy. The current therapeutic strategy focuses on escalating function and obliterating symptoms, especially soreness, as the main symptom and cause of disability.[5] Thus, an alternative is needed to not only alleviate pain but also target some of the biological alteration that are highly desirable in osteoarthritis, namely in cartilage, as well as those that occur around bones, muscles, synovia, and ligaments.[6]

Among the approaches that can potentially positively intervene in reversing or correcting some of these associated pathologies are low-level laser therapy (LLLT) and, more advanced, high-intensity laser therapy (HILT). LLLT was found to significantly alleviate acute and chronic pain conditions such as rheumatoid arthritis, chronic arthritis, carpal tunnel syndrome, and knee injuries. However, HILT recently has become more eminent in physical therapy, which can span and stimulate larger and/or deeper joints that are arduous to reach with LLLT. HILT is a new, painless, and powerful modality that significantly alleviate pain. With its photochemical, photothermal, and photomechanical actions, HILT has many therapeutic steads, including analgesic, anti-edema, and biostimulation effects. HILT is acceptable in treating pain, but its analgesic effect in osteoarthritis has been poorly studied.[7] Currently, research on the effects of HILT in patients with knee OA is still finite, so this study aims to compare the effectiveness of High-Intensity Laser Therapy (HILT) and Low-Level Laser Therapy (LLLT) in functional enhancement in patients with knee OA.

METHODS

This research was a quasi-experimental pretest and posttest with controlled group design. 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 diagnosed with bilateral grade 2–3 knee OA based on Kellgren-Lawrence classification, with a body mass index >18 dan <24 Kg/m2, mild pain (VAS 0–3), no contraindication for laser therapy, and agreed to participate in this study. Patients with an acute inflammatory condition of the knee joint, cardiovascular disease profile, uncontrolled hypertension, (systolic blood pressure >130 mmHg and/of diastolic blood pressure >90 mmHg), neurological disorders affecting balance, cognitive nuisance (MoCA-INA score <26), visual and vestibular 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, or currently taking drugs that can affect balance were excluded from the study. Any patients in which during the study period did not complete the program, had a serious dermatologic reaction after receiving laser therapy, or decided not to continue the program were dropped out of the study. Consecutive sampling was used as the method of sampling, with a minimum of 15 subjects in each group, calculated with 95% confidence level and 90% power of test with expected drop-out of 20%.

The participants' baseline data included age, gender, education level, BMI, duration suffering from OA, MoCA-INA score, and level of physical activity were obtained in the time of enrollment. The participants were then randomly allocated into 2 groups, HILT and LLLT. HILT was given using High Intensity Laser Device BTL-600 in 2 phases; phase 1, aimed to induced 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, aimed to elicit biostimulation, 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 admit 2 laser therapy sessions a week for 4 weeks. Knee functional status was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) before and after treatment was conducted. KOOS is a clinical outcome assessment for young, middle-aged, and elderly adults with knee injuries and/or knee OA, which commonly used to observe the clinical course and outcome of the disease after intervention. The patients were instructed to fill out the KOOS questionnaire that contain five subscales of questions; pain, other symptoms, daily life activities, sports and recreation functions, and quality of life related to the knee.[8]

This research has obtained an ethical clearance from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University Semarang and from the Research Ethics Committee of RSUD K.R.M.T. Wongsonegoro, Semarang City. All research subjects had asked for their consent by signing a written informed consent. 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 stipulate differences between groups. A paired t-test was used to analyzed the disparity before and after treatment in each group. The p value <0.05 with a 95% confidence interval were considered as statistically significant.

RESULTS

Thirty-four patients were initially enrolled in this study, and 4 participants (3 with BMI >24 kg/m^2 and 1 with VAS pain >3) were excluded from this study. Of the 30 participants who had the initial measurement, 1 participant from the HILT group and 2 participants in the LLLT group were dropped out due to lost in follow-up. A total of 14 participants in the HILT group and 13 participants in the LLLT group were analyzed. Demographic analysis showed no significant diversity in patient's mean age, gender, education level, BMI, length of time suffering from OA, MoCA-INA score, and level of physical activity between groups, which indicates similar characteristic in the two groups.

Analysis was conducted on each subscale of KOOS score (Table 2). Paired analysis of pain, other symptoms, and daily life activities subscales showed a significant difference in HILT and LLLT groups, while unpaired analysis of each of those subscales showed a significant

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
Knee Functional Improvement Analysis

Variables	Intervention	Laser Therapy		*p*
		HILT	LLLT	
Pain	Pre treatment	57.9 ± 4.78	59.0 ± 5.02	0.575§
	Post treatment	68.5 ± 3.03	63.5 ± 4.99	0.006§*
	p	<0.001¶*	<0.001¶*	
	Difference	10.6 ± 2.62	4.5 ± 0.52	<0.001‡*
Other Symptoms	Pre treatment	60.6 ± 5.13	61.5 ± 5.09	0.655§
	Post treatment	73.2 ± 3.24	64.9 ± 4.96	<0.001§*
	p	<0.001¶*	<0.001¶*	
	Difference	12.6 ± 2.47	3.4 ± 0.51	<0.001‡*
Daily life activities	Pre treatment	54.6 ± 3.86	54.0 ± 5.02	0.571§
	Post treatment	64.9 ± 3.18	58.1 ± 5.02	<0.001§*
	p	<0.001¶*	<0.001¶*	
	Difference	10.3 ± 1.33	4.1 ± 0.86	<0.001‡*
Sports and recreation	Pre treatment	28.0 ± 2.22	27.2 ± 1.63	0.272§
	Post treatment	34.6 ± 3.57	29.9 ± 1.85	<0.001§*
	p	<0.001¶*	<0.001¶*	
	Difference	6.6 ± 3.48	2.8 ± 0.44	0.001‡*
Quality of Life	Pre treatment	54.6 ± 3.11	57.0 ± 2.83	0,044§*
	Post treatment	64.4 ± 3.34	62.4 ± 2.79	0.110§
	p	<0.001¶*	<0.001¶*	
	Difference	9.8 ± 0.43	5.4 ± 0.51	<0.001‡*
KOOS Score	Pre treatment	51.1 ± 3.56	51.7 ± 3.84	0.680§
	Post treatment	61.1 ± 3.18	55.8 ± 3.81	0.001§*
	p	<0.001¶*	<0.001¶*	
	Difference	9.9 ± 1.02	4.0 ± 0.18	<0.001‡*

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

disparity in post-treatment and delta score between each group. The results indicates that the patients who admit HILT treatment experienced significantly greater enhancement than those who admit the LLLT intervention. Paired analysis on quality of life subscale showed a significant divergence in both groups, and the unpaired analysis showed a significant divergence in pre-treatment and delta score between each group. Post-treatment KOOS score were significantly different between the two groups, which is higher in HILT group. The delta KOOS score from pre- and post-treatment were significantly divergence, with HILT group gained a larger amendment in the KOOS score.

DISCUSSION

The result of this study indicated an enhancement in clinical symptoms that was greater in the HILT group. The result was in line with a meta-analysis by Ahmad *et al* that showed a greater effect of HILT on reducing pain, based on the VAS score, compared to the control group.[9] Improved clinical outcomes can be attributed to the effect of laser therapy, which is associated with biostimulation and anti-inflammatory properties at the tissue and cellular level.[10] Photon energy from the emitted laser is absorbed by the photoreceptors of the mitochondrial respiratory chain complex (cytochrome-c oxidase,

porphyrin, and flavoprotein), which yields high-energy molecules for optimal tissue and cellular function. Throughout this process, reactive oxygen species are also induced at low levels, stimulating various transcription products of genes responsible for anti-inflammatory activities. The high-intensity laser can also endow a large amount of energy output in a relatively short time and has deeper penetration than LLLT. Deep tissue penetration with scattered laser radiation allows HILT to exhibit a photo-thermal effect that triggers local tissue relaxation and positive blood flow changes, diminish edema. Thus, the application of HILT can yield in more favorable alleviation of knee OA symptoms and deduct treatment time compared to LLLT.[11,12]

On the daily activity subscale, there was a more significant enhancement in the KOOS score in the HILT group compared to the LLLT group. The results of this study are in accordance with the study of Khesie *et al*., which showed that the WOMAC score in patients who admit HILT was significantly better than the LLLT group.[13] The use of KOOS has been deemed more appropriate to assess a patient's quality of life and it can be used to evaluate the functional improvements that were not detected by WOMAC.[14] These findings were reinforced by the study of Kim *et al*., who showed that the functional score of patients with genu OA was better in the group administered HILT therapy than the group administered conventional therapy.[15] Tantamount results were also found on the daily activities subscale, where HILT produced better enhancement than LLLT. Assessment of daily activities in OA patients is critical because the OA condition is characterized by joint degeneration involving articular cartilage and much of the surrounding tissue. A disturbed balance between damage and repair of joint tissue leads to loss of articular cartilage, subchondral bone remodeling, osteophyte formation, ligament laxity, periarticular muscle infirmity, and occasionally synovitis. Joint degeneration in OA results in pain, stilted, and limited movement, thus contributing to inactivity.[16,17]

This study demonstrated a significant enhancement in the sports and recreation activity subscale in the group receiving HILT therapy. This result is in line with the study of Ordahan *et al*., who also discovered a significant increase in the HILT intervention group compared to the LLLT intervention group. Enhancement of function in the sport and leisure activity subscales, such as squatting, kneeling, jumping, twisting/twisting, and running, is a related consideration for sugery in OA patients. Exercise is also a factor which may worsen OA, where any mechanical stress that exceeds the tolerance of articular cartilage can lead progression of joint degeneration.[18]

The post-treatment quality of life subscale score of the HILT group was found to be higher than that of the LLLT group. These results align with the study of Ordahan *et al*., which signify a more significant enhancement in the quality of life subscale score in the HILT group than in the LLLT group.[19] Patients with knee OA tend to experience physical finite, pain, and functional restrictions. As such, these individuals suffer progressively increasing impacts on their daily living activities, leading to losses in work relationships, leisure, social life, and quality of sleep, which also significantly derives their quality of life. Thus, quality of life is one of the factors used to evaluate the impact of the disease.[20]

This research has a limitation. The evaluation of functional enhancement is only done once, after the 8th treatment, so it cannot assess how long the effectiveness of HILT and LLLT can last in increasing patient functional improvement.

CONCLUSION

The administration of HILT could significantly escalate the functional improvement more than LLLT in patients with knee osteoarthritis, which could be crucial in treating patients with a higher activity level and also provides a shorter period of treatment.

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Original Article

Comparison of Protein Energy Wasting Assessment on Quality of Life Regular Hemodialysis Patients

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Abstract

Background : Protein energy wasting (PEW) is one of several markers of the quality of hemodialysis (HD) services in Indonesia, however not many studies conducted PEW assessement with quality of life (QoL) domain of regular HD patients.
Aim: To determine comparison of PEW assessment with QoL domains in regular HD patients.
Methods : A Cross-sectional study with total sampling of 105 regular HD patients at Sanjiwani Gianyar General Hospital, on June to July 2022, The PEW assessments: body mass index (BMI), serum albumin, subjective global assessment (SGA), malnutrition inflammation score (MIS), and the International Society of Renal Nutrition and Malnutrition (ISRNM) with QoL domains by KDQOL-SF (Kidney Disease Quality of Life Short Form).
Results : Most of the subjects were men (54.2%), the mean age was51.66 years and mean duration of HD was 50.28 months. The mean of BMI, serum creatinine, and serum albumin were 23.46 kg/m^2, 9.70 mg/dL, and 3.86 mg/dL respectively, and median MIS 5. This study obtained significant correlation of BMI and QoL domains: work status, physical functioning, role of physics, energy/fatigue, and SF 12 physical composite. The MIS also significantly correlated with emotional well-being, sleep, and burden of disease. And ISRNM significantly correlated with energy/fatigue, and sexual function, On logistic regression analysis, this study obtained that albumin was significantly related to general health, emotional well-being, and energy/fatigue,
Conclusion: Assessment of PEW (BMI, serum albumin, MIS, SGA, and ISRNM) were related to several domains of QoL.

Keywords : Protein Energy Malnutrition, Hemodialysis, quality of life

INTRODUCTION

Patients undergoing hemodialysis (HD) have increased from year to year. In 2015, there were 2.9 million people who needed dialysis in Asia. It is estimated that the number is increasing by more than 10% per year.[1] Based on report of 2018th Indonesian Renal Registry, there are 132,142 people were actively undergoing regular hemodialysis, and the highest proportion was 61.5% at the age of 45–64 years (productive age group).[2] Regular HD patients often experience protein energy malnutrition or protein energy wasting (PEW) complications. Protein energy wasting is a condition of malnutrition and inflammation that occurs simultaneously and is caused by decreased nutritional intake, inflammatory processes, uremic toxins, catabolism processes related to dialysis, metabolic derangements, comorbid diseases, cardiovascular diseases, infections, frailty, and depression.[3] Several studies have been conducted found that the prevalence of PEW in regular HD patients varies between 28–69%.[4,5] This depends on the assessment of PEW diagnosis, such as the simplest PEW measurement BMI, serum albumin levels to the combined measurement of the MIS index, SGA and ISRNM criteria.[6]

Protein energy wasting occurs progressively with decreased kidney function and duration of HD, which will affect to weakness, frailty, decreased response to erythropoietin, and the QoL of regular HD patients.[7] However, there were lack of research in Indonesia that investigated the relationship between PEW and quality of life domain of regular HD patients. Study by Zuijdewijn *et al*. (2015) obtained a significant relationship between SGA, MIS, and the mental domain of quality of life in regular HD patients. The research in Bahrain Manama 2020 found that there was a relationship between the family domain and the psychological domain of the QoL of regular HD patients.[9] Are these various PEW assessments related to the quality of life of regular HD patients in Indonesia? There were not many studies carried out the relationship of PEW and QoL domain. Therefore, it is important to conduct this research to examine the relationship between various PEW assessments by BMI, serum albumin, serum creatinine, SGA, MIS, and ISRNM criteria and the QoL domain of regular HD patients. This study also important in the inflammation and malnutrition influence to the outcomes of regular HD patients and also in nutritional interventions of regular HD patients.

METHODS

This study was a cross-sectional study to determine the prevalence of PEW and its comparison of PEW assessment with QoL domains of regular HD patients at Hemodialysis Unit Sanjiwani Gianyar General Hospital on June to July 2022. Protein energy wasting was assessed by BMI, serum albumin, serum creatinine, SGA, MIS, and ISRNM criteria. The quality of life of regular HD patients was assessed by KDQOL-SF, and then analysed by software SPSS. Correlation of each PEW assessment with each QoL domain were analysed with Pearson correlation and also multivariate analysis by logistic regression. All of the subjects signed the informed consent.

RESULTS

This study was conducted in hemodialysis unit of Sanjiwani Gianyar General Hospital, and a total of 105 patients met the inclusion criteria. This study consisted of 58 (54.2%) men; the mean age was 51.66 years, and the mean length of HD was 50.28 months. All subjects underwent 9 hours HD a week. This study found that the mean of BMI, serum creatinine, and serum albumin were 23.46 kg/m^2, 9.70 mg/dL, and 3.86 mg/dL respectively, and the median MIS was 5. Fifty percent subjects were actively working as farmers, labourers, private workers, and civil servants or armies/police. The main causes of chronic kidney disease were Diabetes Mellitus and hypertension in 46.7% of subjects, followed by chronic glomerulonephritis in 20.6% and chronic pyelonephritis in 20.6% of subjects, as depicted in Table 1.

This study obtained prevalence of PEW based on BMI <18.5 kg/m^2, albumin <3.8 mg/dL, MIS >5, SGA B and C, and ISRNM ≥=2 were 7.6%, 40%, 47.6%, 41%, and 41%respectively. Body mass index is the simplest parameter in this study, but it is less capable of determining PEW in CKD patients with multifactorial aetiology. The biochemical parameter of serum albumin is almost the same as the SGA criteria and MIS composite criteria as well as the standard PEW criteria with ISRNM in detecting malnutrition. In our study assessment of quality of life in CKD patients using KDQOL-SF. The subject's quality of life consists of several domains as described in Table 2. This study found the mean of overall health and general health were 68.57 ± 20.96 and 59.18 ± 18.62 respectively, the cognitive status mean 71.49 ± 16.86 and quality of social interaction 77.90 ± 15.56, social support and dialysis staff encouragement were 85.71 ± 21.41 dan 90.60 ± 12.11. The effect of kidney disease were 69.72 ± 16.91, while the work status, emotional well-being, role of limitation-physical and low of energy/fatigue were 2.86 ± 32.64, 34.36 ± 16.98, 24.76 ± 34.41, dan 31.75 ± 40.66, as listed in Table 2.

This study examined the relationship between PEW and quality of life domain of regular HD patients. Base on Pearson correlation analysis, this study obtained that BMI was significantly correlated with work status with r= -0.356 at p = 0.018, physical functioning with r= 0.036 at p=0.015 and role of physic with r=0.327 at p=0.030.

TABLE 1
Baseline Characteristics

Variable		Percentage (%)	Mean±SD
Age			51.66 ± 12.15
Sex (♂ Man)		55.2	
Duration of HD (months)			50.8 ± 30.99
Etiology of CKD	Type 2 DM	21.5	
	Hypertension	26.2	
	CGN	20.6	
	CPN	20.6	
Serum creatinine			9.70 ± 2.85
Albumin			3.86 ± 0.38
BMI			23.46 ± 2.88
MIS	≤ 5	52.4	
	> 5	47.6	
SGA	A	59	
	B	38.1	
	C	2.9	
ISRNM	Mild malnutrition	40.0	
	Moderate malnutrition	32.4	
	Severe malnutrition	8.6	

HD = *hemodialysis;* CKD = *chronic kidney disease,* BMI = *Body mass index;* MIS = *malnutrition inflammation score,* SGA = *subjective global assessment,* ISRNM = *International society of renal nutrition and malnutrition,* CGN = *chronic glomerulonephritis,* CPN =*Chronic Pyelonephritis*

In this study, the PEW assessment was classified into good and poor quality of base on the median values of each domain. It was found that high albumin (>3.8 mg/dL) was significantly associated with good overall health (>70) with OR=2.6 (CI 95 = 1.19–5.95) at *p*= 0.026. High albumin was also significantly associated with good general health (> 60) with OR 2.46 (CI 95 = 1.08–5.58) with logistic regression analysis it was obtained that high albumin was significantly associated with good general health with ExpB = 2.464 (CI95 = 1.028–5.909) in *p*=0.43. High albumin is also associated with good emotional function with B = 2.451 (CI95= 1.044–6.187) at *p*=0.40, good social function with B = 3.034 (CI95=1.234–7.458) at *p*=0.16. and fatigue, with B = 2.419 (CI95= 1.002–5.836) at *p*=0.49. as in Table 4.

DISCUSSION

This study investigated the prevalence of PEW and its relationship with quality of life domain in regular HD patients. PEW assessment which included BMI, albumin, MIS, SGA and ISRNM criteria is associated with each quality of life domain is new in this study. This study found that the prevalence of PEW based on albumin <3.8 g/dL, MIS >5, SGA B and C, and ISRNM ≥2 were 7.6%, 40%, 47.6%, 41%, and 41% respectively. The prevalence of PEW in this study was found to be lower than several other studies which found that the prevalence of PEW in Southeast Asia was 52.8% by MIS or SGA.[4] While, BMI <18.5, is less sensitive to assess PEW, that It had multifactorial aetiology, however this study obtained the prevalence of PEW is lower than the study that conducted anthropometrically in Ethiopia (23.4%).[10] A study conducted in Malaysia by Harvinder *et al* in 2016 found a higher prevalence of PEW as assessed by ISRNM criteria was 59%, while the prevalence of PEW with an MIS value ≥5 higher was 88% in regular HD patients. In Harvinder's study, it was found that the HD duration of most patients was more than 5 years (68%)[11] whereas in our study the mean HD duration was 50 months (<5 years) which could influence inflammation in PEW. In our previous study found PEW by ISRNM criteria was

TABLE 2
The Quality of Life Domains of Subjects

Quality of Life Domains	Mean±SD
Overall health	68.57 ± 20.96
Symptom problem list	69.72 ± 16.91
Effect of Kidney Disease	67.65 ± 17.07
Burden of kidney Disease	42.14 ± 23.67
Work status	32.86 ± 32.64
Cognitive status	71.49 ± 16.86
Quality of Social interaction	77.90 ± 15.56
Sexual function	79.26 ± 27.00
Sleep	61.79 ± 16.25
Social Suport	85.71 ± 21.41
Dialisis staff encouragement	90.60 ± 12.11
Patient Satisfaction	70.32 ± 17.60
Physical functioning	58.71 ± 26.10
Role of limitation-physical	24.76 ± 34.41
Pain	69.05 ± 22.09
General health	59.18 ± 18.62
Emotional well-being	34.36 ± 16.98
Role limitation-emotional	31.75 ± 40.66
Social function	65.36 ± 20.60
Energy/ Fatigue	43.48 ± 17.50
SF 12 physical-composite	41.49 ± 8.79
SF 12 mental composite	35.13 ± 7.13

66.2% and 69% by MIS ≥5.[5] This study found a lower prevalence of PEW compared to previous studies because in the last 2 years we carried out a fluid and nutrition maintenance training program for caregivers of HD patients. All of the subjects in this study underwent intermittent HD for 9 hours a week and this study obtained better medians for several domains of subject quality of life than other studies. The mean of overall health, cognitive status, quality of Social interaction, sexual function, sleep and general health were 68.57 ± 20.96, 71.49 ± 16.86, 77.90 ± 15.56, 79,26 ± 27.00, and 61.79 ± 16.25, 59.18 ± 18.62 respectively. This study also analyzed each quality of life domain and found an overall health average of 68.57, better than reseach conducted at Sanglah General Hospital in 2020 of 62.17.[12] This study included subjects with a mean age similar to the study at Sanglah General Hospital, but the domains of social function (65.36 vs 62.71), physical function (65.36 vs 55.08) and sexual function (79.26 vs 26.25) were better in our study than in the Sanglah study. The characteristic difference in this study is that there were fewer male subjects (55%) compared to Sanglah General Hospital (66.6%). Our research was conducted in the district area, while Sanglah's research was conducted in the provincial capital, so further research is needed regarding the relationship between social factors and sexual relations with the quality of life of regular HD patients.[12]

Our study also analyzed between each PEW assessment and the QoL domain, we found that MIS was negatively significant correlated with emotional well-being, sleep and burden of disease. That meant lower MIS (≤5) was correlated with better emotional well-being, sleep and burden of disease rather than the patients with higher MIS (>5). In a study conducted by Bilqic *et al* in Ankara, Turkey, found that patients who had a high MIS >8 had greater sleep disturbances compared to those with

TABLE 3
Correlation of PEW with quality of life domains

PEW assessement	Quality of life domains	r	*p*
BMI	Work status	-0.356	0.018
	Physical functioning	-0.363	0.015
	Role of physic	-0.327	0.030
	Energy/fatique	-0.374	0.012
	SF 12 phisic composite	-0.428	0.004
Serum Albumin	No quality of life domains were significantly correlated		
MIS	Emotional well-being	-0.331	0.028
	Sleep	-0.311	0.040
	Burden of disease	-0.349	0.020
ISRNM	Energy /fatique	-0.349	0.020
	Sexual function	-0.383	0.010

TABLE 4
Logistic Regression Analysis of PEW with Quality of Life Domains

PEW Assessment/Quality of Life domain		ExpB	CI95%	*p*
BMI	Burden of disease	0.232	0.66-0.818	0.023
	Role of physics	0.208	0.059-0.731	0.014
	SF 12 Mental	0.141	0.035-0.573	0.006
Abumin	General health	2.464	1.028-5.909	0.043
	Emotional	2.541	1.044-6.187	0.040
	Role of emotional	3.034	1.234-7.458	0.016
	Fatigue	2.419	1.002-5.836	0.049
MIS		–	–	–
SGA		–	–	–
ISRNM		–	–	–
ISRNM	SF 12 Mental	0.211	0.048-0.918	0.038

an MIS <6.[13] Other study that conducted by Visiedo *et al* and Rambod *et al* found that patients who had PEW, also had lower emotional well-being, that is similar with our study.[14,15]

This study also investigated the relationship between PEW based on ISRNM criteria with energy/fatigue and sexual function as QoL domain. Our study found that SF 12 mental was significantly related to ISRNM criteria. That is similar with the previous studies by Viseido *et al*, that found a significant relationship between mental SF 12 and malnutrition with ISRNM criteria.[14] That meant our study supported that higher PEW score by ISRNM criteria was related to lower SF 12 mental score as QoL domain.

Meanwhile, this study obtained the anthropometry with BMI is significantly negatifve correlated with mean work status, physical functioning, energy/fatigue, and SF 12 physics. and also found significantly with burden of disease, role of physics and SF 12 mental. However the influence of BMI is not too

strong on the quality of life domain. Other studies have examined the relationship between BMI and quality of life, such as research by Apple R *et al*. which found that BMI was significantly related to physical and mental roles. That meant our study found that there were relationship between BMI in obese patients and lower physical functioning scores.[16,17]

CONCLUSION

The prevalence of PEW in this study was lower than other similar studies. BMI is significantly correlated to Burden of disease, role of physics and SF 12 mental, Albumin is significantly correlated to general health, emotional, role of emotional and fatigue. MIS also significantly correlated to emotional well-being, sleep and burden of disease. Criteria of ISRNM were significantly correlated to fatigue and sexual function. However this study did not found significant correlation of SGA and QoL domains. We should continue this study by case control study of PEW assessment the QoL of HD patients.

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Original Article

The Effect of Coenzym Q10 on Doxorubicin-induced Cardiotoxicity in Non Hodgkin's Lymphoma Patients

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Abstract

Background : Non-Hodgkin's Lymphoma is a primary malignancy in the Lymph Nodes and lymphoid tissue originating from B lymphocytes, T lymphocytes and Natural Killer (NK) cells. Therapy for Non-Hodgkin's Lymphoma chemotherapy can be given alone or combined with radioactive therapy. Doxorubicin is a chemotherapy drug used for lymphoma with side effects, one of which is cardiotoxic effects. The aims of this study was to prove that coenzyme Q10 can reduce the cardiotoxic effect of doxorubicin chemotherapy in non-Hodgkin's lymphoma patients

Methods : Intervention study with a randomized pre and post test double blind control group design with 34 NHL patients undergoing chemotherapy. The treatment group received additional therapy with coenzyme Q10 300mg/day for 12 weeks while the controls received placebo. The cardiotoxic effects examined were assessed based on the results of Electrocardiography and Echocardiography.

Results : The treatment group with coenzyme Q10 supplementation after the 4th chemotherapy showed a decrease in echocardiography results in 3 patients (18%) and in the control group 17 patients (100%). There was a significant difference in the echocardiography results of the treatment and control groups (p=0.001). There were no drug side effects in both groups

Conclusion : Coenzyme Q10 supplementation provides an improvement in the cardiotoxic effects of doxorubicin in non-Hodgkin's lymphoma patients, on echocardiography, but not on Electrocardiography.

Keywords : Hodgkin's non lymphoma, Doxorubicin, Cardiotoxicity, Coenzym Q10

INTRODUCTION

Malignant tumors in lymph nodes and lymphoid tissues arising from B lymphocytes, T cells, and NK cells are known as non-Hodgkin's lymphoma (NHL).[1] Non-Hodgkin's lymphoma accounts for 90% of lymphoma cases worldwide, and 509 new cases of NHL are recorded worldwide.[2] NHL ranks sixth among the most common malignancies in Indonesia.[2] Chemotherapy is the treatment of choice for LNH, the management of patients with NHL, according to the clinical practice guidelines adapted to the National Comprehensive Cancer Network (NCCN),[3] mainly using first-line chemotherapy namely cyclophosphamide, doxorubicin, oncovin/vincristine and prednisone + rituximab (CHOP ± R).[1,3]

An anthracycline chemotherapy drug, doxorubicin, has a side effect that is considered serious for the heart, dilated cardiomyopathy. This side effect can lead to treatment discontinuation and increased morbidity.[4,5]

Hequet *et al*. reported that 27.65% of patients receiving doxorubicin at an average cumulative dose of 300 mg/m^2 met the criteria for subclinical cardiomyopathy, and only one of these patients developed congestive heart failure.[6] Research by Khattry *et al*. showed that 27% of patients experienced a decrease in left ventricular ejection fraction >10% with the use of doxorubicin 300–450 mg/m^2.[7] Chung *et al*. reported that as many as 29 of 174 patients (16.7%) experienced a decrease in ejection fraction >10% or a decrease in left ventricular ejection fraction below 55% of the normal limit without symptoms of heart failure. Research by Kamelia at Cipto Mangunkusumo Hospital shows an average decrease in left ventricular ejection fraction.[4]

Coenzyme Q10, also known as ubiquinone, is an important nutrient in the regulation of enzyme activities to carry out various biochemical reactions that have an effect on the decrease in ATP production through inhibition of glycolysis. Coenzyme Q10 (CoQ10) or ubiquinone is a lipophilic molecule commonly found in cell membranes, known as a cofactor that transfers electrons from complexes I and II to complex III during ATP formation in the inner mitochondrial membrane. In addition, CoQ10 may also act as an antioxidant in the cell membrane. The underlying pathophysiology of cardiotoxicity is increased free radical production, lipid peroxidation, and reactive oxygen species (ROS) accumulation can damage myocardium, and CoQ10 may prevent myocardial damage by inhibiting oxidative stress and lipid peroxidation.[8]

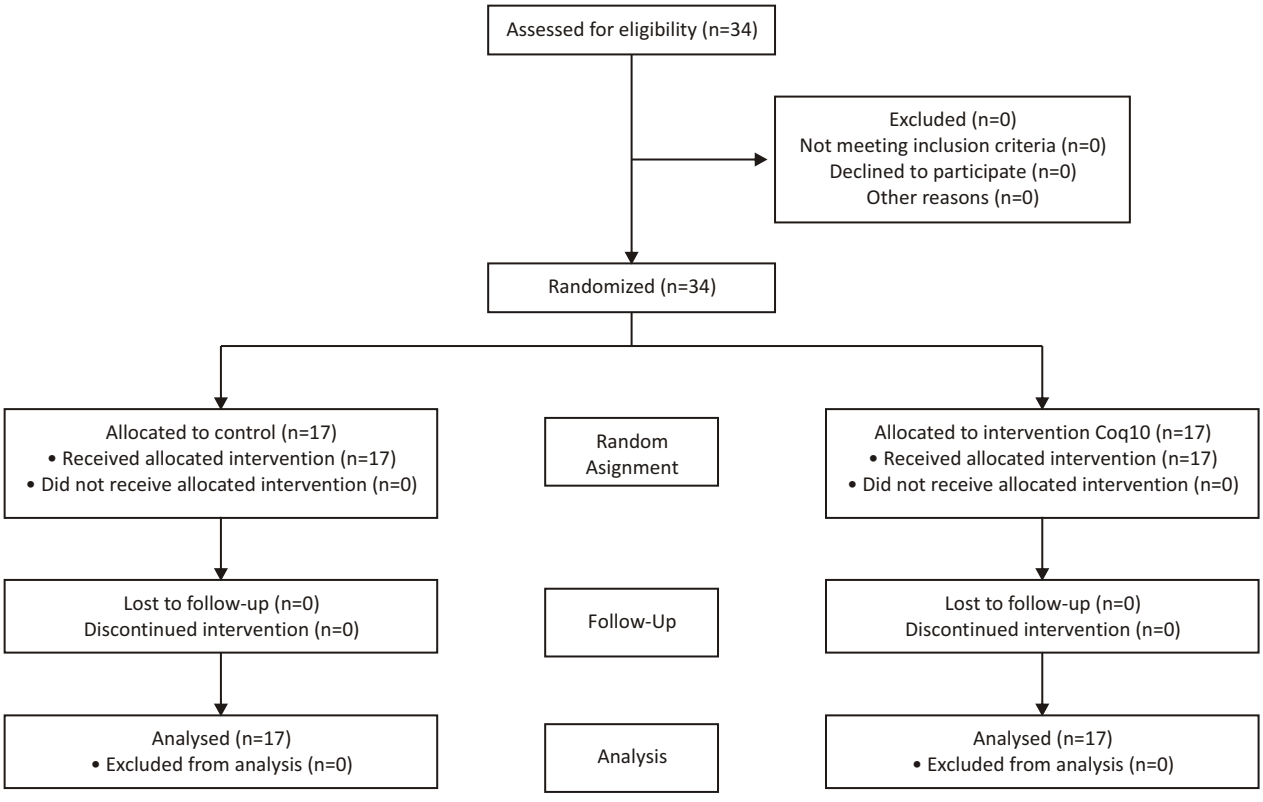
Coenzyme Q10 supplementation on cardiotoxic effects in NHL patients receiving doxorubicin chemotherapy at Dr. Kariadi Hospital, Semarang has never been studied before.

METHODS

This study is an interventional research with randomized pre- and post-test double-blind control group design. The research subjects were LNH patients who received chemotherapy with 12 weeks of therapy. The sample that has been determined is 34 samples. The data was collected from December 2022 to May 2023. The research group was divided into 2 groups, namely the treatment group (NHL patients who received chemotherapy and coenzyme Q10 300 mg/day) and the control group (NHL patients who received chemotherapy and placebo in the same capsule form). The study sample size was calculated using the intervention-test sample size formula, paired numerical, with an error rate of $\alpha = 5\%$, two-way hypothesis testing, then $Z\alpha = 1.65$. The study power is 80%, $Z\beta = 0.84$, the significant difference in value is 1.9. Therefore, N = 17 patients were obtained for each group.

Electrocardiographic examination prior to chemotherapy and echocardiography after the fourth cycle of chemotherapy. Inclusion criteria were all NHL patients with normal sinus rhythm and normal systolic function (>50%) or left ventricular ejection fraction. Chemotherapy-appropriate laboratory values were obtained and patients agreed to participate in this study. Exclusion criteria included history of antioxidant use, comorbidities (diabetes mellitus, hypertension, previous heart disease), and history of left chest irradiation. The independent variable was coenzyme Q10, while the dependent variable was left ventricular ejection fraction on echocardiography and the first negative wave deflection whose width exceeded 0.04 seconds accompanied by inverted T or pathological Q waves. The dependent variables were the echocardiographic left ventricular ejection fraction and the pathological Q wave, and the independent variable was coenzyme Q10. The coenzyme Q10 treatment group received 300 mg capsules/24 h for 12 weeks starting one week before chemotherapy, the control group received placebo capsules/24 h for 12 weeks starting one week before chemotherapy. The subjects received doxorubicin chemotherapy with an interval of three weeks before a second blood sample was taken one week after the second series of doxorubicin chemotherapy.

Subject characteristics were presented descriptively consisting of gender, age, type of NHL and type of chemotherapy. The relationship between variables was analyzed using normality test, Chi-Square test, Shapiro-Wilk test and normality data, then hypothesis testing on pre-post test using paired t-test. This study was approved by the Health Research Ethics Commission of Dr. Kariadi Hospital Semarang .



Picture 1. Consort Flow Diagram

RESULTS

This study included 34 NHL patients receiving doxorubicin chemotherapy divided into 17 control and 17 coenzyme Q10 treatment groups, sample characteristics shown in Table 1.

Table 1 shows that the majority of the control and treatment groups were male. There were no differences in the basic clinical characteristics between the control and coenzyme Q10 groups in terms of medical history, symptoms and signs, physical examination, laboratory results, and medical therapy.

Table 1 shows that the majority of the control and treatment groups were male. The ages under 60 years with the most type of NHL is DLBC and chemotherapy received CHOP.

Table 2 shows the results of ECG data analysis before and after the 4th chemotherapy, comparing two variables. There was an insignificant relationship between the two groups of NHL patients who received doxorubicin and coenzyme Q10 chemotherapy (p >0.05), which means that the confounding variables were homogeneous.

Table 3 in treatment group, echocardiographic changes pre and post chemotherapy using paired T-test, obtained significant results (p<0.05). Similarly, in control group, echocardiographic changes pre and post chemotherapy fourth cycle obtained significant results (p<0.05). The results of data analysis showed that treatment group pre chemotherapy had echo results around 67.65±5.44 and post chemotherapy fourth cycle around 61.06±5.03, so the difference between pre chemotherapy and post chemotherapy fourth cycle in treatment group was around 6.58±4.07. The control group pre chemotherapy with echo results 69.65 ± 6.38 and echo results post chemotherapy fourth cycle were about 55.18 ± 4.69. So the difference between pre and post chemotherapy fourth cycle in the control group was about 14.47 ± 6.66. The difference results in the control group were greater than the treatment group. This showed significant results that the control group had a greater difference.

The results of the Saphiro-Wilk normality test showed normal distribution of all data. In the treatment group before chemotherapy amounted to 0.063 (p>0.05), control amounted to 0.377 (p>0.05). In the treatment group after the 4th chemotherapy was 0.923 (p>0.05) and control was 0.10 (p>0.05).

The results of unpaired t-test showed no significant difference in the treatment and control groups pre chemotherapy, while there was a significant difference in the treatment and control groups post

TABLE 1
Subject Characteristics

Variable		n	%
Group	Intervention	17	50
	Control	17	50
Gender	Man	19	55.9
	Woman	15	44.1
Age	≤ 60	27	79.4
	≥ 60	7	20.6
Histopathology	DLBCL	20	58.9
	NKT, Nasal type	6	17.6
	Burkitt Lymphoma	2	5.9
	Diffuse Follikuler	6	17.6
Type of Chemotherapy	CHOP	22	68
	RCHOP	12	32
	ECG before Chemotherapy		
	No pathological Q waves	34	100

TABLE 2
The Relationship between ECG Results in the Chemotherapy Group with Coenzyme Q10 Supplementation and the Control Group after the Fourth Chemotherapy Session

Variable	ECG Result post fourth chemotherapy				*p*
	Pathological Q waves		No pathological Q waves		
Group	n	%	n	%	
Intervention	3	9	14	41	0.128
Control	7	21	10	29	

*Significant ($p < 0.05$), Chi Square test

chemotherapy fourth cycle and the difference between the groups pre and post chemotherapy fourth cycle. The results of the paired t-test showed significant differences in the treatment and control groups pre and post chemotherapy fourth cycle.

DISCUSSION

Non-Hodgkin lymphoma is a malignancy of the lymphatic tissue and is the sixth most common malignancy in Indonesia.[9] Based on histological type, it is divided into two major groups, namely Non-Hodgkin lymphoma, which is the most common case in head and neck cancer, and Hodgkin lymphoma.[1] NHL can originate from B lymphocytes, T lymphocytes, and, although it is very rare, from natural killer (NK) cells in the lymphatic system.[9] NHL is the seventh most common cancer and the ninth most common cause of cancer death in Indonesia.[10] The incidence of LNH at Dr. Kariadi Central General Hospital (RSUP), Semarang in January 2015 to May 2017 recorded the highest incidence, which was 60 cases.

The most common gender was male in both control and treatment groups in this study, less than 60 years of age was the largest age group. The most common histopathology in this study was DLBCL, consistent with a previous study in Southeast Asia (2017) that the most common histopathology in LNH was

TABLE 3
Difference in Echo results pre chemotherapy and post chemotherapy fourth cycle

Echo Result	Intervention	Control	*p*
Pre Chemotherapy	Mean 67.65 ± 5.44	Mean 69.65 ± 6.38	0.333‡
Post Chemotherapy	Mean 61.06 ± 5.03	Mean 55.18 ± 4.69	<0.001‡
p	0.000†	0.000†	

*Significant (p<0,05); ‡ unpaired t-test; † paired t test

DLBCL.[11]

Chemotherapy is the treatment of choice for NHL according to Clinical Practice Guidelines (CPG) and the National Comprehensive Cancer Network (NCCN),[3] involving first-line chemotherapy with Cyclophosphamide, doxorubicin, Oncovin/Vincristine, and Prednisone+ Rituximab (CHOP ± R).[1,3] Chemotherapy drugs, such as doxorubicin, are known to have serious side effects on the heart (cardiotoxicity). These side effects can lead to treatment discontinuation and increased morbidity.[4,5] Chung *et al*. reported that out of 174 patients, 29 (16.7%) experienced a decrease in ejection fraction >10% or a decrease in left ventricular ejection fraction below 55% of the normal limit without symptoms of heart failure.[4,10] Heart damage due to doxorubicin results from oxidative production in the heart, mainly in cardiac mitochondria. In mitochondria, the formation of oxygen radicals occurs through the auto-oxidation of doxorubicin semiquinone. Hydrogen peroxide is also a cause of oxidative stress and is responsible for inducing apoptosis by doxorubicin in endothelial and cardiac muscle cells. Hydrogen peroxide is inactivated by two enzymes, catalase, and glutathione peroxidase. Cardiac muscle contains a small amount of catalase, so the activity of glutathione peroxidase plays an important role in neutralizing the effects of anthracycline and free radicals formed.[12] The main mechanism of doxorubicinol toxicity occurs due to its interaction with iron and the formation of reactive oxygen species (ROS) that damage cellular macromolecules.[13] Heart damage caused by doxorubicin is due to oxidation in the heart. Mitochondria are the primary target of cardiotoxicity in the heart. Increased production of oxygen radicals. Hydrogen peroxide also causes oxidative stress and apoptosis induction by doxorubicin in endothelial and cardiomyocyte cells.[14] Damage to heart cell organs leads to myocardial damage, resulting in myocardial dysfunction. Examinations that can be performed include electrocardiography, angiography, echocardiography, and cardiac enzyme tests, but the examination recommended by the European Society for Medical Oncology (ESMO) is echocardiography.[15,16]

Coenzyme Q10 is the primary coenzyme for ATP in mitochondria and functions as an intracellular antioxidant, protecting mitochondrial protein membranes and phospholipids from free radicals. CoQ10 also acts as a membrane antioxidant. The pathophysiology underlying cardiotoxicity involves increased production of free radicals, lipid peroxidation, and accumulation of reactive oxygen species (ROS) that can damage the myocardium. CoQ10 is expected to prevent myocardial damage by inhibiting oxidative stress and lipid peroxidation.[8]

Based on this research, coenzyme Q10 can be used as an adjunctive therapy to mitigate cardiotoxic effects in patients undergoing Doxorubicin chemotherapy. This is evidenced by the significant improvement in echocardiographic findings in the treatment group before and after the fourth chemotherapy cycle with additional coenzyme Q10 therapy. Furthermore, this is reinforced by the comparison of echocardiographic results between the treatment and control groups, revealing significant disparities. Although the nonsignificant findings in the Electrocardiogram (ECG) are attributable to reversible changes, often observed within 24 hours of drug administration and subsequently resolving spontaneously.

The findings of this study align with prior research, suggesting that pretreatment with Coenzyme Q10 at a dosage of 100 mg/kg for 18 days exhibits protection against cardiac hypertrophy and cardiotoxicity, while also reducing lipid peroxidation in rats. Al Qahtani Abdullah *et al*. reported that out of the initial search yielding 11,303 articles, 14 were included. Among these 14 articles, 10 indicated that Coenzyme Q10 offers protective effects against doxorubicin-induced cardiotoxicity.[17]

CONCLUSION

Coenzyme Q10 can be considered as an adjunctive therapeutic option for NHL patients undergoing doxorubicin chemotherapy to prevent myocardial damage, thereby reducing cardiotoxic effects and lowering morbidity. However, this study requires further investigation with a longer duration, extending to the completion of 6 cycles of chemotherapy, to provide a clearer understanding of the cardiotoxic effects in NHL

patients receiving standard doxorubicin chemotherapy combined with Coenzyme Q10 therapy. Given that cardiotoxic assessments are not limited to EKG and ECHO, further research using cardiac enzymes is necessary to comprehensively evaluate cardiotoxic effects.

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Original Article

Differences in Effectiveness between Progressive Muscle Relaxation Therapy and Slow Deep Breathing Therapy on Elderly Sleep Quality

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Abstract

Background : Every individual has a lifetime, starting from the womb, born into the world, to becoming elderly. Aging is a process of gradual loss of tissue's ability to repair itself, maintain its normal structure and function so that it cannot defend the tissue from injury (including infection), and repair the damage that occurs. In the elderly, there are various kinds of health problems such as sleep disorders. Sleep disorder or insomnia is a person's inability to sleep. Poor sleep quality can be improved in various ways such as relaxation techniques. This study was aimed to compare the effectiveness of Jacobson's Progressive Muscle Relaxation (JPMR) and Slow Deep Breathing Therapy in improving sleep quality in the elderly.
Methods : This type of research was a quantitative quasi-experiment with pretest and post-test methods (one group pre-test and post-test design). Respondents involved 49 people while research data were processed with the Mann-Whitney and Wilcoxon tests. The Sleep Quality Questionnaire used the PSQI questionnaire.
Results : The Wilcoxon test with an alternative to the Mann-Whitney test showed no significant difference in effectiveness between the two therapies with p-value = 0.274.
Conclusion : Both therapies had almost the same level of effectiveness; there was no significant difference between the two, so progressive muscle relaxation therapy and Slow Deep Breathing were equally effective in treating anxiety and improving sleep quality.

Keywords : Elderly, Sleep Quality, Progressive Muscle Relaxation, Slow Deep Breathing

INTRODUCTION

Every individual has a period of life from the womb to becoming elderly or aging. Aging can be defined as the process of slowly losing the ability of tissues to repair themselves and maintain their normal function.[1] Based on data, several provinces in Indonesia in 2021 have experienced an old population structure, including 8 provinces with more than 10 percent of the population aged. One of these provinces is Central Java with a percentage of 14. Seventeen percent of the elderly population. The elderly population is dominated by the female population and is more numerous in urban areas. In terms of age, the elderly are divided into three types. This makes, in 2021 alone, there are more than 17 percent of people included in the pre-elderly group. This data showed that pre-elderly group who will enter the old age population needs to receive more attention.[2]

Sleep disorder or insomnia is one of the various health problems that can threaten the health of the elderly. Insomnia itself is also often defined as a person's inability to sleep.[3] In elderly patients, insomnia can be divided into three types, namely Sleep Onset Problems, Deep Maintenance Problems, and Early Morning Awakening.[4] According to several studies that have been conducted related to insomnia in elderly patients, the results showed that the risk of elderly people experiencing insomnia is higher than patients who are still young.[5,6] Sleep disorders like this can be addressed in two ways, one of which is non-pharmacological therapy in the form of relaxation that can reduce anxiety, muscle tension, and reduce pain.[7] JPMR or Jacobson's Progressive Muscle Relaxation can be an option in performing relaxation techniques. This technique can reduce tension, pain, relieve pain, and reduce anxiety.[8]

In addition to JPMR relaxation techniques, Slow Deep Breathing therapy can also be performed to train the body and mind comprehensively based on diaphragmatic breathing,[9] so that it is expected to improve the quality of sleep of the elderly. Based on several previous studies, it is concluded that the quality of sleep of the elderly often decreases with age. Therefore, this study would be conducted to examine the difference in effectiveness between progressive muscle relaxation therapy and Slow Deep Breathing therapy on the quality of sleep of the elderly. The purpose of this study was to examine whether there is a difference between the use of progressive muscle therapy and Slow Deep Breathing therapy on elderly sleep quality variables. In addition, it is also to examine the effectiveness of each technique on the quality of elderly sleep.

METHODS

This research was conducted at the Pucang Gading Social Service House Semarang in June 2023. The research was carried out after obtaining approval from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Muhammadiyah University, Semarang. The type of research conducted was a quantitative quasi-experiment. The research subjects consisting of 49 elderly people were divided into two groups with different treatments. The first group would be given progressive muscle relaxation therapy. Meanwhile, the second group would be given Slow Deep Breathing therapy. The elderly involved in this study were selected through several inclusion and exclusion criteria. Some of the inclusion criteria include elderly ≥ 60 years old, residing in the Pucang Gading Semarang Social Service House, and willing to become respondents. Meanwhile, the exclusion criteria included elderly with language and communication disorders or aphasia, hearing impairment, chest pain symptoms, and symptoms of shortness of breath. Through the calculation of Slovin, the number of samples in this study was 53 samples. After the research was conducted, there was 4 samples who dropped out because they did not take part in the study twice in a row. The sampling technique used was Non-Probability Sampling, namely Purposive Sampling. The independent variables in the study were progressive muscle relaxation therapy and Slow Deep Breathing therapy and the dependent variable was the quality of elderly sleep.

The tools used in the study included a tensimeter, stopwatch, respondent form data, and other tools. Meanwhile, the materials used were 49 samples of elderly patients at the Home of Social Service Pucang Gading in Semarang. Data processing started with coding data, transferring data to a computer, cleaning data, to presenting data in numerical, graphical, and pictorial forms.[10] Data analysis techniques that would be used were Univariate Analysis and Bivariate Analysis.

ANALYSIS

Univariate Analysis

Based on the table above, the characteristics of respondents involved in this study include type of therapy, gender, age, latest education, marital status, occupation, and sleep quality before and after therapy. This study provided progressive muscle relaxation therapy to 49% of respondents, namely 24 elderly people. Meanwhile, the rest were given Slow Deep Breathing therapy. This study also found that there were more elderly women than elderly men, as many as 29 people. Respondents were dominated by elderly people who did not work as much as 98%. The last education of respondents was dominated by elementary school graduates as many as 22 people or 45%, elderly who were married as many as 46 people or 94%, good elderly sleep quality as much as 22% and poor as much as 78%. This data showed that the majority of elderly people still had

TABLE 1
Characteristics of Elderly Respondents at the Home of Social Service Pucang Gading, Semarang Based on Variables

Variable		Progressive Muscle Relaxation Therapy	Slow Deep Breathing Therapy	%
Gender	Male	10	10	41%
	Female	14	15	59%
Age	60 – 70	8	17	51%
	71 – 80	16	8	49%
Latest education	SD	13	9	45%
	SMP	6	12	37%
	SMA	5	4	18%
Marriage status	Married	23	23	94%
	Unmarried	1	2	6%
Work	Not Working	24	24	98%
	Retired	0	1	2%
Pre-test sleep quality	Good	9	11	40%
	Poor	15	14	60%
Post-test sleep quality	Good	17	21	78%
	Poor	7	4	22%
Total		24	25	100%

TABLE 2
Wilcoxon Test Analysis Results Pre-test sleep quality to Post-test Progressive Muscle Relaxation Therapy

Variable	n	Mean	Standard deviation	Minimum	Maximum	*p value*
Pre-test	24	7.08	2.545	4	15	0.000
Pos-test	24	4.92	1.840	2	10	

TABLE 3
Results of Wilcoxon Test Analysis of Sleep Quality Pre-test against Post-test Slow Deep Breathing Therapy

Variable	n	Mean	Standard deviation	Minimum	Maximum	*p value*
Pre-test	25	6.6	2.309	4	12	0.000
Pos-test	25	4.4	1.443	3	8	

difficulty or sleep disorders.

Before conducting a sleep quality questionnaire interview, respondents were given a sleep hygiene questionnaire to change their lifestyle and environment to improve sleep quality.[11] Based on the sleep hygiene homogeneity test, a significance of 0.789 was found which showed a value greater than 0.05 as a significant level. Therefore, it was concluded that the groups with the therapy technique had the same variance.

Bivariate Analysis

Bivariate analysis in this study was carried out with the Wilcoxon test because the research data was included in non-parametric data or categorical data. Tabel 2 shows

TABLE 4
Mann-Whitney Test Analysis Results of Progressive Muscle Relaxation Therapy and Slow Deep Breathing Therapy on Elderly Sleep Quality

Variable	n	Mean Ranks	*p value*
Progressive Muscle Relaxation Therapy	48	52.66	0.274
Slow Deep Breathing Therapy	50	46.47	

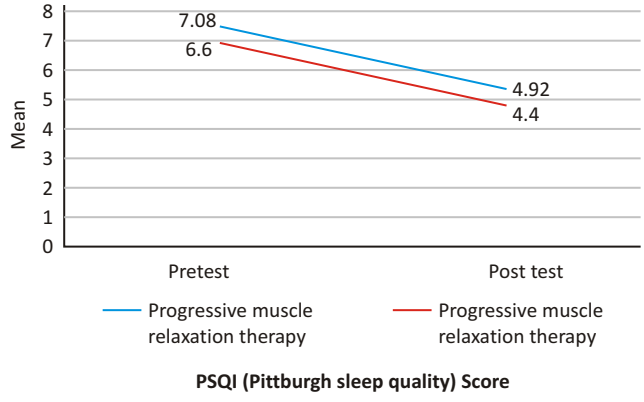

Figure 1. Average of Pre-Test and Post-Test PSQI Score

the test results.

Based on the two tables above, the results showed that there was an effect caused by progressive muscle relaxation therapy and Slow Deep Breathing therapy on the quality of elderly sleep at the Home of Social Service House Pucang Gading Semarang. Both techniques had a significant effect on the quality of sleep of the elderly in the location of this study (Table 3).

Based on the results of the table above, it was found that there was no significant difference between progressive muscle relaxation therapy and Slow Deep Breathing therapy. This was indicated by the *p-value* >0.274 (Table 4).

DISCUSSION

Progressive Muscle Relaxation Therapy on Elderly Sleep Quality

In general, the elderly experience a shortening of sleep time due to the aging process which results in a decrease in sleep quality. This leads to worsening sleep quality. Based on the table previously presented, it was found that the quality of sleep of the elderly who received progressive muscle relaxation therapy has improved. Before the therapy, the mean was 7.08 which then became 4.92 after completion of therapy. This figure shows an increase in sleep quality in the elderly. This is in line with several previous studies, such as those conducted by Rostinah and Tri and Heba Abdel Fatah Ibrahim. Both studies found that progressive muscle relaxation therapy had a positive impact on improving sleep quality and reducing anxiety.[12]

This technique can make a person relax their muscles and feel more comfortable. This will then put the individual in a relaxed stage, resulting in a decrease in emotional reactions.[13] The results of paired t-test research found that paired t-test of elderly sleep quality before and after therapy got $p = 0.0000$, because $p < 0.005$, there is an influence caused by progressive muscle relaxation techniques on the quality of sleep of the elderly.

Slow Deep Breathing Therapy on Elderly Sleep Quality

Slow deep breathing therapy can cause a decrease in sympathetic and increased cardiac output which ultimately results in a decrease in heart rate, cardiac output, vascular tone, and blood pressure. Other impacts that arise are stress reduction and increased positive emotions.[14] In the previous table, it was shown that the quality of elderly sleep has improved after the elderly get this therapy. Based on the table, the average result obtained before therapy was 6.6 and changed to 4.4 after receiving therapy. Research conducted by Febriansyah said that 16 respondents (80%) had good sleep quality after being given slow deep breathing therapy. According to Yanti, it shows that there is an effect of slow deep breathing therapy on headaches and vital signs in hypertension sufferers.[15]

This technique can also increase the interaction

between the brain with psychological flexibility, connecting the parasympathetic with the central nervous system, and activities related to emotional control. This can result in increased positive emotions and reduced anxiety.[16] A decrease in pulse rate, respiration, and blood pressure may also occur.[17] The results of the paired t-test research found that, the *p-value* = 0.000. Because the *p-value* <0.005, there was an influence between Slow Deep Breathing therapy and the quality of elderly sleep.

Deep Breathing Therapy on Elderly Sleep Quality

In progressive muscle relaxation therapy, the mechanism of action was based on the sympathetic and parasympathetic nervous systems. A relaxed state makes a person secrete CRH and ACTH. Thus, the activity of the sympathetic nerves decreased, followed by a reduction in adrenaline and non-adrenaline hormones. The work of the heart would also slow down which makes blood pressure decrease. Meanwhile, in Slow Deep Breathing therapy, there was an increase in baroreflex sensitivity that controls heart rate, heart contraction strength, and blood vessel size. This therapy could also reduce blood pressure.[14]

In Table 4, it is explained the calculation of the different test results between the two techniques. The results obtained were the mean results of the pre-test and post-test sleep quality of progressive relaxation muscle therapy was 52.66. Meanwhile, Slow Deep Breathing gets a score of 46.47. It was found there was no significant difference between progressive muscle relaxation therapy and Slow Deep Breathing therapy, this was indicated by the *p-value* >0.274. Through these scores, it is concluded both types of therapy had the same level of significance and effectiveness in terms of improving the quality of sleep of the elderly.

CONCLUSION

Based on the research that has been performed, it can be concluded that progressive muscle relaxation therapy and Slow Deep Breathing therapy both influenced improving the quality of sleep of the elderly at the home of Social Service Pucang Gading Semarang. Furthermore, there was no significant difference between the two types of therapy in improving the quality of sleep of the elderly at the home of Social Service Pucang Gading Semarang.

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Original Article

Effect of Genistein-rich Edamame Extract on Eosinophil-Lymphocyte Ratio Experimental Study on Atherosclerosis Induced Male Rats

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Abstract

Background : Atherosclerosis is associated with hypercholesterolemia and inflammation. Edamame, a high-genistein soybean variant, is believed to have protective effects against atherosclerosis. This study aimed to determine the influence of edamame extract rich in genistein on the eosinophil-lymphocyte ratio (ELR) levels in rats induced with atherosclerosis.
Methods : This research utilized a true experimental design with a post-test only control group. Thirty male rats were divided into five groups: negative control, positive control, treatment 1 with edamame extract supplementation, treatment 2 with edamame extract rich in genistein supplementation, and treatment 3 receiving atorvastatin. After 28 days, the ELR levels were examined from rat blood. Data were analyzed using One-Way ANOVA - Bonferroni, Kruskal-Wallis Mann-Whitney, and Pearson correlation tests.
Results : There were no significant differences in ELR levels ($p>0.05$) among all treatment groups compared to the negative and positive control groups. T-tests between the negative control and positive control groups, as well as between the positive control and the three treatment groups successively, showed non-significant results (p: 0.376; 0.856; 0.169; 0.066).
Conclusion : The administration of edamame extract rich in genistein did not significantly reduce inflammation levels in blood vessels compared to edamame extract alone, as indicated by non-significant results in the ELR difference analysis.

Keywords : Genistein Rich Edamame, Eosinophil-Lymphocyte Ratio

INTRODUCTION

Atherosclerosis is an inflammatory disease of the arteries characterized by imbalance and abnormal accumulation of lipids, inflammatory cells, matrix deposits and proliferation of smooth muscle cells in the walls of medium and large caliber arteries. Atherosclerotic lesions are very susceptible to occurring in the curves of blood vessels and their branches.[1] The manifestation of atherosclerosis is atherosclerotic vascular disease (AVD), which is a serious contributor to mortality and morbidity in the world compared to other diseases.[2] In Indonesia, AVD ranks first among the cardiovascular diseases that have high mortality and morbidity rates.[3] According to the Health Research and Development Agency, Ministry of Health of the Republic of Indonesia, the death rate due to manifestations of AVD is 12.9% of all deaths.[4]

Inflammation plays an important role in every stage of atherosclerosis, from the beginning of plaque development to plaque rupture which can cause thrombosis.[5,6] Previous research showed that eosinophils and lymphocytes have a role in inflammation, atherosclerosis and endothelial dysfunction. The eosinophil to lymphocyte ratio (ELR) is a novel inflammatory biomarker that has been demonstrated to show an association between ELR and poor outcomes in patients with cancer. ELR was also found to be a predictor of the severity of isolated coronary artery ectasia.[2,7]

Prevention efforts through early detection of risk factors and control efforts are very important. One of them is through limiting the consumption of fats and types of food that have anti-hypercholesterolemic effects, one of which is soybeans. Edamame is a variant of soybeans that has a higher isoflavone content than other food crops.[8] In Indonesia, edamame is widely known and consumed together with other food ingredients.[9] Genistein is an isoflavone that is abundant in Edamame, has the potential to prevent atherosclerosis by suppressing blood vessel inflammation. Studies on the effect of genistein on inflammatory markers are still very limited. Therefore, in this study, researchers wanted to determine the effect of administering genistein edamame (Glycine max (L) Merrill) on the eosinophil lymphocyte ratio levels in male rats *(Rattus novergicus)* which were induced by atherosclerosis.

METHODS

Research Design

This research is a true experimental research with post test only with control group design. Edamame extract (Glycine max (L) Merrill) rich in genistein administered to mice with induced atherosclerosis and administration of atorvastatin as a positive control, while the outcome was the level of eosinophil lymphocyte ratio.

Research Sample

Male *rattus novergicus* rats aged 15 weeks, with body weight around 180–200 grams were selected as the inclusion criteria. Mice were kept in stainless steel cages with a 12-hour light cycle. Rat food was given ad libitum. The minimum sample size is determined based on Federer's experimental sample size formula, namely (t-1) (r-1) ≥ 15, where t is the number of treatment groups and r is the sample size for each treatment group.[10] In this study, there were four treatment groups and one control group. From this formula, it was determined that the sample size for each group was 6 mice. Thus, the total number of samples in this study was 30 mice.

Time and location of Research

Research and data collection were carried out for 2 months. This research was carried out in three places, namely the STIFAR Semarang Laboratory as a place for making experimental materials, LPPT FK UGM as a place for treatment of experimental animals and RSH Prof Soeparwi for analysis of eosinophil lymphocyte ratio levels in mice.

Research Variable

The independent variable of this research is edamame extract (Glycine max (L) Merrill) rich in genistein and the dependent variable is eosinophil lymphocyte ratio levels.

Research Implementation

Thirty male Sprague Dawley rats that met the inclusion and exclusion criteria were adapted for 7 days. Sample group 1 as a negative control (K-) was not given any treatment apart from being given standard food and drink ad libitum. Group 2 as a positive control (K+) was injected with adrenaline 0.006 mg/200 gr BW once on the first day and egg yolk was given on the following day at a dose of 5 gr/200 gr BW once a day every day for 28 days. Sample group one (P1) received treatment similar with that in the positive control group, but with added edamame extract rich in genistein 38mg/200 gr BW. Second group (P2) received treatment similar with that in the positive control group, but with added edamame extract rich in genistein 5mg/200 gr BW. Meanwhile, the third group (P3) was given treatment similar with that in the positive control group, with an addition of atorvastatin 1.5mg/ 200gr BW. After 28 days, eosinophil lymphocyte ratio (ELR) levels were measured.

The standard edamame extract process begins with drying for 3 days, weighing, maceration with MeOH, filtering with a rotary evaporator, then evaporation using a water bath. Extraction was carried out using n-hexane, collecting the extract, and measuring the genistein levels in it.[10,11] ELR calculations were carried out from the results of peripheral blood smears, calculated in the acute phase (< 4 hours). Blood smears were made using Giemsa staining method. The smear

was aired until dry, then dripped with methanol for 5 minutes, stained using drops of Giemsa that had been diluted with phosphate buffer (1:4) for 30 minutes. The preparations are then rinsed with distilled water and dried. Leukocyte count were observed in blood smears using a binocular microscope at 100x objective magnification with the addition of immersion oil. The differential count was carried out in an area where the erythrocytes were evenly distributed. ELR was calculated from the ratio between the number of eosinophils and lymphocytes from the peripheral blood smear.[12]

Data Analysis

Data obtained from research observations are in the form of eosinophil lymphocyte ratio levels. The data was tested for normality using Shapiro Wilk test, then continued with statistical testing. The data normally distributed were tested with ANOVA, while data not normally distributed were tested with Kruskal-Wallis test. The *p value* of significant differences was <0.05. If the test results show that H0 fails to be rejected (no differences between groups are found), a post hoc test is not carried out, if a difference is found, a post hoc test is carried out. The post hoc test carried out depends on the results of the Test of Homogeneity of Variances. If the same variance is obtained (significance value >0.05), a post-hoc test is carried out using the Bonferonni method. If different variations are obtained (significance value <0.05), a post-hoc test is carried out using Games-Howell. Data processing was carried out with SPSS 25 for Windows software.

RESULTS

Measurement of Genistein Rich Edamame Extract

After going through extraction and collection process, genistein content was calculated in genistein-rich edamame extract by comparing the standard genistein reagent. Genistein levels were found to be 78% of the total extract composition.

***Eosinophil-Lymphocyte Ratio* (ELR)**

Shapiro-Wilk and Levene Test showed the data was normally distributed and homogeneous, so difference test was continued with one-way ANOVA. The ELR results data are displayed in Table 1, while the comparison between groups is presented in the bar graph in Figure 1.

From ELR data, it can be seen that there are inconsistencies in ELR results, where the ELR value was highest in the negative control group and the lowest in treatment group 3. Giving genistein rich edamame extract did not reduce ELR levels more than edamame extract alone, in fact it was significantly higher compared to edamame extract alone. However, this difference was not statistically significant. Because the results of the one-way ANOVA test were not significant, a post-hoc test was not carried out.

T-test was carried out between the negative control group and the positive control group, as well as between the positive control group and the three treatment groups as shown in Table 2. There were no significant results between the negative control group

TABLE 1
ELR Analysis

Group	ELR Mean ± SD	*p**
K-	0.1115 ± 0.1015	0.435
K+	0.0087 ± 0.1593	
P1	0.0170 ± 0.1597	
P2	0.3135 ± 0.0511	
P3	0.0042 ± 0.0065	

Description: *Significant ($p < 0.05$)

TABLE 2
LSD Post HOC test

Group	K-	K+	P1	P2	P3
K-	–	0.376	–	–	–
K+	–	–	0.856	0.169	0.066

Description: *Significant ($p < 0.05$)

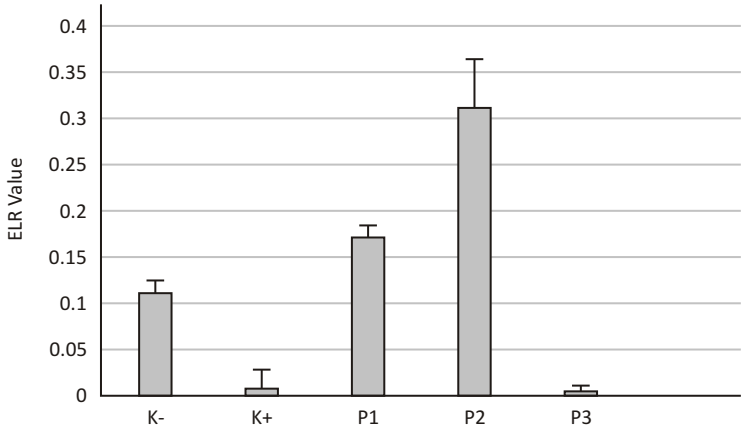

Figure 1. ELR Value Bar Graph

and the positive control group.

DISCUSSION

Genistein is claimed to exert many beneficial effects on health, such as protection against osteoporosis, reduction in the risk of cardiovascular disease, alleviation of postmenopausal symptoms and anticancer properties. Apart from that, genistein exerts evident anti-inflammatory properties by affecting granulocytes, monocytes, and lymphocytes that can serve as a novel source of potential phytotherapeutic agents for anti-inflammatory therapies.[14]

Genistein in edamame has an effect of inhibiting the formation of atherosclerotic lesion by becoming an active ingredient that inhibits proliferation of TGF-β1 cell signal. It has anti atherogenic properties in blood vessels, antiplatelet aggregation, help oncrease excretion of bile acids or neutral sterol and interferes with the formation of micelles. Genistein also has an active form from tyrosine kinase inhibitor. It plays an important role in LDL cholesterol catabolism.[15]

The eosinophil-to-lymphocyte ratio (ELR) is a new inflammatory bioindex that takes into account both eosinophil and lymphocyte levels. Eosinophils and lymphocytes have been implicated in inflammation, atherosclerosis, and endothelial dysfunction in previous investigations. An increased ELR was closely related to inflammation and atherosclerosis.[16,17]

Eosinophil-Lymphocyte Ratio (ELR) data in this study has been analyzed using statistical tests. ELR is the ratio between the number of eosinophils and lymphocytes in blood, which reflect the inflammatory response in the body. The results of statistical tests, including the Shapiro-Wilk test and Levene Test, showed that the ELR data had a normal and homogeneous distribution, so one-way ANOVA was chosen as the difference test. However, the ANOVA test did not show significant differences between groups, with p value of 0.435. High variability in ELR results was seen in negative control group which showed the highest value, while treatment group 3 (P3) showed the lowest value. Although there were inconsistencies in these results, the differences were not statistically significant.

In previous studies there was an association between ELR and cardiovascular health, especially in patients with isolated coronary artery ectasia (CAE) who showed higher ELR.[7] Eosinophils, as the main component of ELR, have role in inflammatory responses and atherosclerosis. Previous studies suggest that increased eosinophil counts may be associated with the risk of future cardiovascular events. Another study found elevated serum levels of immunoglobulin E, basophils, and eosinophils in patients with coronary artery disease compared with healthy control subjects. Other studies also show that eosinophil cationic protein (ECP), which is a sensitive marker of eosinophil activation, is associated with coronary atherosclerosis.[4] Eosinophils can exhibit pro-atherosclerotic properties through proteins stored in prominent cytoplasmic granules. In previous studies, it was found that eosinophils are involved in inflammatory processes and endothelial dysfunction, strengthening the argument that ELR may reflect cardiovascular health conditions.[1,4] Although not statistically significant, the high variability of ELR in the study groups is interesting and indicates variability in response of inflammation that may influence cardiovascular prognosis.

This study has several limitations involving the concentration of genistein-rich edamame extract used in this study were not able to differentiate the effect of multiple doses on the test parameters. This research was only carried out for four weeks, so there is still bias because the process of atherosclerosis in mice occurs at a different rate than in humans, yet it can't determine the final results (end-point surveillance).

CONCLUSION

Administration of genistein rich edamame extract did not significantly reduce inflammation severity in blood vessels compared to edamame extract alone (p = 0.435) as indicated by non-significant results in the ELR difference analysis.

Ethical Approval

This research has been approval by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University with Ethical Clearance.

Conflicts of Interest

The authors declare no conflict of interest.

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Author of Contributions

RDP, EB, AS were involved in planning and supervised the work, RDP performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. RDP performed the xyz calculations and statistical analysis. RDP, EB, AS aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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Original Article

Comparing the Pulmonary-Spirometry in Laboratory Workers Who Wear Acchadana® and KN95® Masks

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Abstract

Background : The upper respiratory tract is susceptible to inflammation caused by exposure to airborne contaminants, particularly chemical irritants. Inhaled irritant gases can lead to various symptoms and adverse reactions in the respiratory tract. Laboratory workers are at a high risk of respiratory tract inflammation due to exposure to volatile chemicals. The use of personal protective equipment (PPE), such as masks, is essential to prevent inflammation and protect the respiratory tract. Lung function tests using spirometry, including Forced Vital Capacity (FVC), Forced Expiratory Volume in One Second ($FEV_{1.0}$), and Peak Expiratory Flow (PEF), can help identify abnormalities in lung function. The primary objective of this investigation is to juxtapose the pulmonary conditions of laboratory workers before and after the utilization of KN95® masks and Acchadana® masks.
Methods : The study design was a Randomized Control Trial, and the subjects were divided into two groups: the control group wearing KN95 masks and the treatment group wearing Acchadana® herbal masks. Spirometry measurements were taken before and after using the masks, and statistical analysis was conducted to compare the results.
Results : The results showed that both mask groups experienced improvements in lung function parameters after using the masks. However, the KN95 mask group showed better lung conditions compared to the Acchadana® mask group.
Conclusion : Spirometry tests conducted on lab workers revealed improved lung function metrics (including FVC, $FEV_{1.0}$, and PEF) following the usage of KN95 masks and Acchadana® herbal masks. The KN95 mask users exhibited superior respiratory health compared to the other group in this investigation.

Keywords : Personal Protective Equipment, KN95 mask, Acchadana, Spirometry, Lung function

INTRODUCTION

The upper respiratory tract is the first line of direct exposure to various airborne contaminants and susceptible to sustain inflammation.[1] Pollutants in the form of chemical irritants that evaporate in gas form are the most likely triggers to inflammation and other adverse reactions in the upper and lower respiratory tract. The number of inhaled irritants will give different symptoms and body responses such as excess mucus production, breathing discomfort, impaired lung function, and other severe symptoms.[2,3]

The lungs are the organs most vulnerable to chemical irritant substances. The effects caused by inhaling irritant gases are highly dependent on the level of concentration and duration of exposure. Dissolved irritant gas causes a burning sensation and other manifestations such as eye, nose and bronchial irritation.[4] Inhalation of irritant gases such as chlorine, ammonia, sulfur dioxide and hydrogen chloride causes irritation of the mucous membranes in the upper respiratory tract.[4] These conditions synergistically trigger hypersecretion.[1,5] Common responses to inhalation of various irritant gases include inflammation, edema and sloughing of the epithelium which, if left untreated, can lead to scar formation and remodeling of the lung and airways.[6]

Laboratory workers are the group that uses the most volatile chemicals, the risk of experiencing inflammation of the upper and lower respiratory tract is higher than workers in other sections.[1,3] The easiest way to prevent inflammation of the respiratory tract and lungs is by using personal protective equipment (PPE) in the form of a mask.[1,3] The use of PPE in environments with exposure to chemicals allows for upper respiratory tract protection, so that gases or chemical vapors in the air are not easily inhaled. Continuous inhalation of reactive chemicals can result in decreased lung function.[1,3]

At a certain period of time, it is important for laboratory workers to carry out examinations to find out whether lung spirometry is normal or not.[7] Abnormalities in lung function can be identified by carrying out lung function tests using spirometry, one of which is forced vital capacity (FVC), forced expiratory volume at 1 second ($FEV_{1.0}$) and peak expiratory flow (PEF).[8] However, the interpretation of pulmonary function examination results is influenced by several factors, namely gender, age, height, ethnicity, body surface mass of an individual.[9,10]

The efficacy of personal protective equipment (PPE) in the form of masks necessitates a consideration of their quality and protective capabilities. The safeguarding of the respiratory tract against exposure to airborne pollutants, encompassing both particulate matter and gases, is suboptimal when employing conventional cloth masks alone. Empirical evidence establishes that KN95® masks and herbal Acchadana® masks exhibit comparable efficacy in protecting the respiratory tract. Notably, a comparative analysis revealed that, over a span of two months, the utilization of herbal masks resulted in a statistically significant increase in mean FVC, $FEV_{1.0}$, PEF when contrasted with ordinary cloth masks.[11] Consequently, it was deduced that herbal masks exhibit superior efficacy in enhancing lung function. The primary objective of this investigation is to juxtapose the pulmonary conditions of laboratory workers before and after the utilization of KN95® masks and Acchadana® masks.

METHODS

Study Design

This research was a Randomized Control Trial, with a purposive sampling technique. The subjects were 50 laboratory workers from different laboratories (blood service, blood component, serology-hematology and infection). Each laboratory was taken half randomly and divided into two groups. The control group wore KN95® masks (n=25) and the treatment group wore Acchadana® herbal masks (n=25, 1 drop out). Each subject received a mask according to the group, which was given periodically every two weeks.

The inclusion criteria involved subjects who were in good health condition based on the results of a doctor's examination, and who were willing to participate in research by signing informed consent. Exclusion criteria included subjects who were pregnant, heavy smokers, had consumed alcohol and had a history of respiratory problems, allergic rhinitis and asthma. Masks produced by CV. Beauty Kasatama Surabaya. The research subjects wore masks for 60 days (maximum of 8 hours/day), then were examined for spirometry.

Spirometry measurement

Pulmonary function parameters measured in this study were Forced Vital Capacity (FVC), Forced Expiratory Volume in One Second ($FEV_{1.0}$), and Peak Expiratory Flow (PEF). Measurement of pulmonary function parameters was done using Medical International Research Spirolab III portable spirometer before and after using mask. This research has received approval from the Ethics Commission of the Faculty of Medicine UNDIP with number 152/EC/KEPK/FK-UNDIP/VI/2022.

Acchadana® Herbal Mask and KN95® Mask

Herbal mask extract Acchadana® *Nephrolepis exaltata* – *Hibiscus rosa sinensis* was made at the Diponegoro University Applied Sciences Laboratory. Acchadana® masks have received brand patents with No. IDM000921225 and KN95® Masks with coded GB2626-2006.

Statistical analysis

Data normality test from each group was analyzed using the Shapiro-Wilk test. The mean differences between FVC, $FEV_{1.0}$, and PEF values before and after treatment in both groups were analyzed using paired-t Test since all data showed normal distribution. Data that were not normally distributed were analyzed by the Mann-Whitney Test, a significant difference test if p <0.05.

RESULTS

Subjects participating in this study consisted of 79.6% male and 20.4% female. The research subjects were divided into 2 groups of masks, namely KN95 masks which consisted of 80% men and 20% women. In the Acchadana® herbal mask group, 79.2% were men and 20.8% were women. In the KN95® mask group there were 8% of subjects with a history of smoking, while in the Acchadana® herbal mask group there were 16.7% of subjects. There were only 2 (8%) subjects with respiratory problems in the KN95® mask group. In the Acchadana® herbal mask group, all subjects had no history of respiratory problems (Table 1).

The paired difference test of the FVC pre-test and FVC post-test in Table 2 showed that the KN95 mask group increased significantly with a *p-value* = <0.001 (p <0.05), while the Acchadana® mask group experienced an increase but not significantly statistics with a *p-value* = 0.051. The results of the unpaired different test on FVC pretest group between KN95 and Acchadana® showed no significant difference. There is a significant difference in FVC between KN95® and Acchadana® *p-value* = 0.042 (p<0.05). The difference in FVC values between the KN95® and Acchadana® mask groups was presented in the box plot diagram in Figure 1.

The results of the paired difference test $FEV_{1.0}$ pre-test and $FEV_{1.0}$ post-test increased significantly in both mask groups (p<0.05), KN95 masks *p-value* = <0.001, and Acchadana® masks *p-value* = 0.045. Unpaired different test on $FEV_{1.0}$ pre-test between KN95® and Acchadana® masks there was no significant difference. However, the difference in $FEV_{1.0}$ between the KN95® and

TABLE 1
Demographics and research subject data based on mask groups

Characteristics		Mask					
		KN95®			Acchadana®		
		n	%	Mean ± SD (min–max)	n	%	Mean ± SD (min–max)
Age				33.36 ± 8.93			33.96 ± 9.47
Gender	Man	20	80.0		19	79.2	
	Woman	5	20.0		5	20.8	
Blood pressure	Systolic			130.20 ± 24.45			122.38 ± 21.76
	Diastolic			82.88 ± 10.35			79.33 ± 12.87
Smoking history	Yes	2	8.0		4	6	
	No	23	90.0		20	5	
Respiratory disorders	Yes	2	8.0		0		
	No	23	92.0		24	100	

TABLE 2
Statistical analysis of FVC

Mask	FVC		*p*	Delta
	Pre	Post		
KN95®	71.75 ± 14.72	89.19 ± 22.23	<0.001¶*	17.44 ± 16.45
Acchadana®	75.99 ± 11.14	83.99 ± 19.51	0.051¶	7.32 ± 17.42
p	0.256¥	0.459§		0.459§

Note: *Significant (p < 0.05); ¥ Independent t; § One Way Anova (Welch); ¶ Paired t

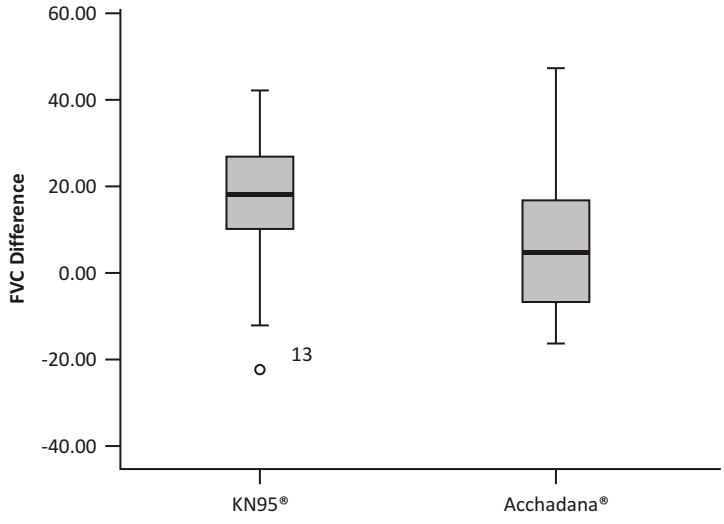

Figure 1. Difference in FVC between groups of KN95® masks and Acchadana® masks

TABLE 3
Statistical analysis of $FEV_{1.0}$

Mask	FEV1		*p*	Delta
	Pre	Post		
KN95®	81.94 ± 16.84	101.14 ± 23.67	<0.001¶*	19.20 ± 18.08
Acchadana®	88.09 ± 13.10	97.30 ± 21.89	0.045¶*	8.39 ± 19.43
p	0.156¥	0.475§		0.049¥*

Note: * Significance ($p < 0.05$); ¥ Independent t; § One Way Anova (Welch); ¶ Paired t

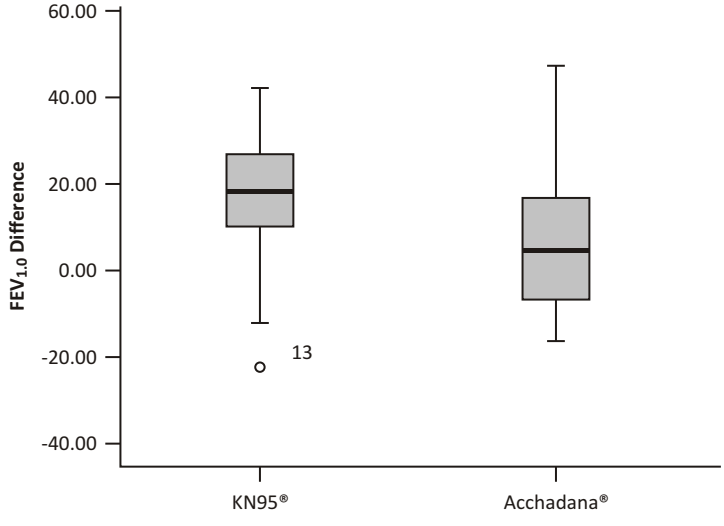

Figure 2. Difference in $FEV_{1.0}$ between groups of KN95® mask and Acchadana® mask

Acchadana® masks was significantly different with a *p-value* = 0.049 ($p < 0.05$) (Table 3). The difference in $FEV_{1.0}$ values between the KN95® mask group and the Acchadana® mask was presented in the box plot diagram in Figure 2.

The results of the paired difference test PEF pre-test and PEF post-test also increased significantly in the two mask groups. KN95® mask and Acchadana® mask have *p-value* = <0.001 and *p-value* = 0.044 ($p<0.05$). There was no significant difference in the results of the unpaired

TABLE 4
Statistical analysis of PEF

Mask	PEF		*p*	Delta
	Pre	Post		
KN95®	89.61 ± 17.86	117.16 ± 36.87	<0.001¶*	27.55 ± 28.36
Acchadana®	97.24 ± 28.25	111.54 ± 26.77	0.044¶*	13.80 ± 31.66
p	0.259¥	0.729§		0.187†*

Note: * Significance (p < 0.05); ¥ Independent t; § One Way Anova (Welch); ¶ Paired t; † Mann Whitney

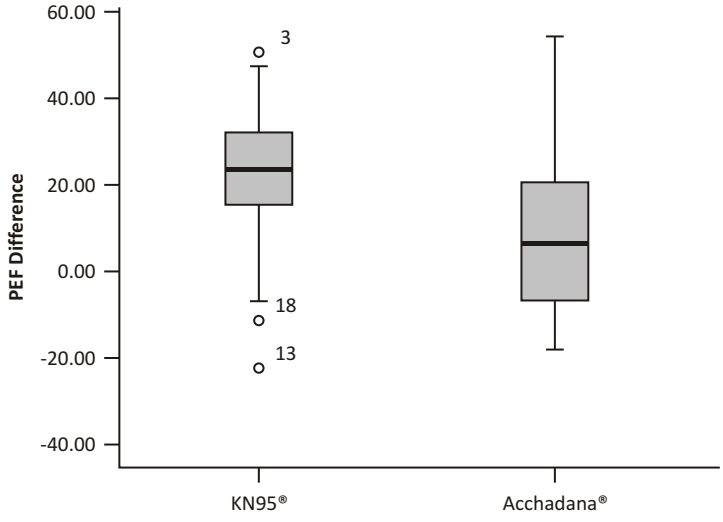

Figure 3. Difference in PEF between groups of KN95® mask and Acchadana® mask

difference test on the PEF pre-test, post-test and delta between KN95® and Acchadana®. The PEF pre-test has a *p-value* = 0.259. Meanwhile, the PEF post-test *p-value* = 0.729, and the PEF delta *p-value* = 0.187 (Table 4).

The difference in PEF values between the KN95® and Acchadana® mask groups was presented in the box plot diagram in Figure 3.

DISCUSSION

This study involved subjects of laboratory workers who were vulnerable to exposure to volatile chemical irritants in the work environment. Twenty-five subjects used KN95® mask and Acchadana® herbal mask while working. Acchadana® herbal mask contains *Nephrolepis exaltata* and *Hibiscus rosasinensis*. Both of these masks have equal protection in protecting the respiratory tract. The use of masks correctly and continuously during the study showed that the condition of the respiratory tract remains good even when working with chemicals. However, unfortunately the chemicals are easily vaporized and are at risk of inhalation. The general cascade of responses to inhaled irritant gases usually begins with inflammation of the respiratory tract epithelium.[12] Apart from causing respiratory allergies such as bronchial asthma and hypersensitivity pneumonitis, exposure to chemicals is reported to cause a series of diseases that interfere with lung function.[2] Exposure to chemicals for a long time and continuously can trigger edema and increase mucus secretion in the respiratory tract. On the other hand, inflammation occurs in the respiratory tract and lung parenchyma resulting in decreased lung function.[11]

Inhalation of pollutants in the air and gases chronically impairs lung function and can cause lung disorders.[13] The parameters tested in the study were the assessment of FVC, $FEV_{1.0}$, PEF. FVC examination is performed to analyze the maximum amount of air that can be exhaled after taking the deepest possible breath. Previous studies reported that patients with airway obstruction and increased expiratory airflow resistance needed 25–30 seconds to expel their entire vital capacity, whereas normal subjects only needed 3 seconds.[14]

In theory, forced vital capacity decreases with age.[15] In this study, FVC in the KN95® and Acchadana® groups both increased after using masks for eight weeks. Apart from the well-protected workers' respiratory tract,

these results are also likely to be influenced by the subject's age, which is around 30 years old on average. In younger individuals, lung function typically peaks, characterized by optimal respiratory capacity and efficiency. However, the interpretation of pulmonary function examination results is also influenced by several other factors, namely gender, height, and ethnicity.[9,10]

It is important to evaluate the volume of air in the first second of expiration. A value of $FEV_{1.0}$ that is reduced by more than FVC is a marker for an obstructive disorder. Measurement of the volume of gas expelled during a 1 second time interval in both mask groups showed a significant increase in the $FEV_{1.0}$ score compared to before using the mask. The percentage of severity of airflow obstruction on the $FEV_{1.0}$ examination in this study was included in the mild category with a value of >80%. Severity is included in the moderate category if the subject's $FEV_{1.0}$ value is at a score of 50–79%, and the severe category if it drops to 30–49%.[7]

Maximum flow rate (PEF) during expiration can also be read on spirometry. Exhaled air in a spirometer is recorded as a spirogram, which is calibrated against volume changes.[14] A decreased PEF value indicates obstruction to airflow in the airways, an indication of asthma with early airway obstruction, and often occurs in restrictive lung disease due to reduced volume.[16,17] The PEF scores of the KN95® mask and Acchadana® mask groups increased significantly after wearing the mask for four weeks. These results indicate no increased airway resistance.

The superior lung function observed in the KN95 mask group compared to the Acchadana® herbal mask group could be attributed to several factors. Firstly, KN95 masks are designed to provide a high level of filtration efficiency, effectively blocking a greater proportion of airborne particles and irritants from entering the respiratory system. This enhanced filtration capability may lead to reduced exposure to irritants, thereby resulting in less inflammation and better lung function over time.

Additionally, KN95 masks are manufactured according to standardized guidelines, ensuring consistent quality and fit, which is crucial for optimal respiratory protection. On the other hand, while Acchadana® herbal masks may offer certain herbal benefits, their filtration efficiency and consistency in protecting against airborne contaminants may not match that of KN95 masks.

This study still had limitations, including monitoring the use of masks and the compliance of each subject during the research. Even though each group of subjects had been given an understanding of adherence to wearing masks during the study period, this was still difficult to control. Measurement of vital capacity when exhaling air must be ensured that the subject really has maximized the impact when exhaling post-inspired air. More investigation is necessary to explore the efficacy of herbal masks in comparison to conventional PPE protocols.

CONCLUSION

Spirometry examination of laboratory workers showed that all lung function parameters (FVC, $FEV_{1.0}$, and PEF) experienced an increase in scores after using KN95 masks and Acchadana® herbal masks. In this study, the KN95 mask group showed better lung conditions.

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Original Article

The Relationship between Cumulative Platinum-Based Chemotherapy Dose and The Occurrence of Ototoxicity in Head and Neck Malignancies

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Abstract

Background : Chemotherapy is a treatment for head and neck malignancies. Hearing impairment is a side effect of chemotherapy, especially caused by platinum-based chemotherapy. Hearing impairment generally occurs at high frequencies after the administration of chemotherapy. The aims of this study was to prove assosciation between cumulative doses of platinum-based chemotherapy and ototoxic events in head and neck malignancies.
Methods : This is a cross-sectional study. The sample is patients with head and neck malignancy receiving platinum–based chemotherapy at Dr. Kariadi Hospital Semarang from March to June 2023. Hearing assessment using pure tone audiometry was performed randomly at all chemotherapy cycles. Data was analyzed with a chi-square test.
Results : Eighty-one subjects (52 male, 29 female), consisting of 71 subjects received cisplatin, and 10 subjects received carboplatin. Ototoxicity occurs in 91.7% of subjects receiving cumulative doses of cisplatin >300mg/m^2 and carboplatin >1500mg/m^2 compared to cumulative doses of cisplatin <300mg/m^2 and carboplatin <1500mg/m^2, which was 46.7% (p = 0.001, CI 1.416–2.725).
Conclusion : There was a significant association between cumulative doses of platinum-based chemotherapy and ototoxicity incidence of head and neck malignancy patients.

Keywords : ototoxic, pure tone audiometry, chemotherapy, platinum

INTRODUCTION

Head and neck malignancies account for 5.3% of the total incidence of tumors worldwide annually. It is estimated that over 800,000 new cases and nearly 500,000 deaths.[1,2] Surgical procedures, radiotherapy, and chemotherapy in various combinations are used to treat head and neck malignancies, depending on the stage and primary location. Chemotherapy, as one of the multimodal curative therapies, can be given concomitantly with radiotherapy to provide a good therapeutic response. Platinum-based chemotherapy is the most widely used and globally accepted chemotherapy drug.[3,4]

Hearing loss is a sensorineural, bilateral, and permanent ototoxic side effect of platinum-based drugs.[5,6] The prevalence of cisplatin chemotherapy-induced ototoxicity varies widely between 11–97% in several studies.[7,8] The prevalence of ototoxicity due to cisplatin chemotherapy in a previous study was 32%.[8] Hearing loss occurs primarily at high frequencies following the administration of high-dose cisplatin. One study mentioned that a cumulative dose of cisplatin over 300 mg/m² and carboplatin over 1500 mg/m² can cause ototoxicity.[8–10] Ototoxicity is assessed using ASHA criteria measured by pure-tone audiometry. The aim of this study is to prove the relationship between the cumulative dose of platinum-based chemotherapy and chemotherapy-induced ototoxicity in patients with head and neck malignancies at Dr. Kariadi Hospital.

METHODS

This research is an observational analytic study with a cross-sectional design. The subjects of the study were patients with head and neck malignancies who visited the Oncology Clinic and Clinical Diagnostic Centre of Dr. Kariadi Hospital and met the research criteria. Subjects underwent pure-tone audiometry examinations at random chemotherapy session. The study period was from March to July 2023. Sampling was conducted using consecutive sampling. Inclusion criteria included subjects who received at least one cycle of platinum-based chemotherapy, aged ≥18 – 65 years, had a baseline audiogram before chemotherapy, and were willing to participate in the study. Exclusion criteria consisted of long-term use of medications (antibiotics, NSAIDs, quinine), patients with chronic otitis media, a history of hemodialysis, changes in chemotherapy regimens, a history of head and neck radiation, and a history of noise exposure. Ototoxicity was assessed using ASHA criteria, defined as an increase in hearing threshold of 20 dB at one frequency or 10 dB at two consecutive frequencies observed in the audiogram. Confounding factors in this study included gender, age, and history of anemia. Data analysis was performed using the chi-square test with SPSS 25.

This study received ethical clearance and approval from the Research Ethics Committee of Dr Kariadi Hospital and the Medical Council of Dr Kariadi Hospital.

RESULTS

Eighty-one subjects who met the inclusion and exclusion criteria were outpatients at the ENT Oncology Department of Dr Kariadi Hospital during the period from March to July 2023. The characteristics of the subjects are listed in Table 1.

Table 1 shows that the percentage of subjects who

TABLE 1
Characteristics of Subjects

Variable		Ototoxicity		Total
		Positive	Negative	
		54 (66.7%)	27 (33.3%)	81 (100%)
Gender	Male	36 (44.4%)	16 (19.8%)	52 (64.2%)
	Female	18 (22.2%)	11 (13.6%)	29 (35.8%)
Age	>40 years old	36 (44.4%)	20 (24.7%)	56 (69.1%)
	≤40 years old	18 (22.2%)	7 (8.6%)	25 (30.9%)
History of anemia	anemia +	11 (13.6%)	3 (3.7%)	14 (17.3%)
	anemia -	43 (53.1%)	24 (29.6%)	67 (82.7%)
Chemotherapy drugs	Paclitaxel-Cisplatin	49 (60.5%)	22 (27.2%)	71 (87.7%)
	Paclitaxel-Carboplatin	5 (6.2%)	5 (6.2%)	10 (12.3%)
Cumulative Dose	Cisplatin > 300mg/m^2, Carboplatin > 1500mg/m^2	33 (40.7%)	3 (3.7%)	36 (44.4%)
	Cisplatin ≤ 300mg/m^2, Carboplatin ≤ 1500mg/m^2	21 (25.9%)	24 (29.6%)	45 (55.6%)

TABLE 2
Relationship between Cumulative Chemotherapy Dose and Ototoxicity

Variable	Ototoxicity						*p*	PR	*r*	CI 95%
	Positive		Negative		Total					
	n	%	n	%	n	%				
Cumulative dose							0.001	1.964	0.404	1.416–2.725
Cisplatin >300 mg/m^2, Carboplatin >1500 mg/m^2	33	91.7	3	8.3	36	100				
Cisplatin ≤300 mg/m^2, Carboplatin ≤1500 mg/m^2	21	46.7	24	53.3	45	100				

TABLE 3
The relationship between gender, age, and history of anemia with ototoxicity

Variable		Ototoxicity						*p*	PR	CI 95%
		Positive		Negative		Total				
		n	%	n	%	n	%			
Gender	Male	36	69.2	16	30.8	52	100	0.512	1.115	0.796–1.563
	Female	18	62.1	11	37.9	29	100			
Age	> 40 years old	36	64.3	20	35.7	56	100	0.496	0.893	0.653–1.221
	≤ 40 years old	18	72	7	28	25	100			
History of anemia	anemia +	11	78.6	3	21.4	14	100	0.496	1.224	0.883–1.698
	anemia -	43	64.2	24	35.8	67	100			

experienced ototoxicity (66.7%) was higher compared to those who did not experience ototoxicity (33.3%). Male gender and age over 40 years were more likely to experience ototoxicity, among which 60.5% used the cisplatin.

Table 2 shows that ototoxicity in the subjects occurred mostly in the group of subjects who received a cumulative dose of Cisplatin >300 mg/m² and Carboplatin >1500 mg/m². The analysis results indicate a significant relationship between the cumulative dose of chemotherapy and ototoxicity (*p-value* ≤0.05). The correlation value obtained, 0.404, indicates a positive relationship, with the strength of the relationship between the cumulative dose and the incidence of ototoxicity being moderate.

Table 3 shows that ototoxicity occurs frequently regardless of gender (both male and female), all age ranges, and whether there is a history of anemia or not. The analysis results indicate that there is no significant relationship between gender, age, and history of anemia with ototoxicity.

DISCUSSION

The characteristics of subjects with head and neck malignancies in this study were predominantly male (64.2%). This is consistent with previous research indicating that males are 2–4 times more likely to develop head and neck malignancies compared to females.[11] The patients in this study were mostly in the age group >40 years (69.1%) compared to the age group ≤40 years (30.9%), which aligns with research suggesting that head and neck malignancies are more common in the over 50 age group than in younger age groups. This could be attributed to advanced age and higher exposure to smoking and alcohol in males compared to younger individuals and females.[12] On the contrary, other studies have suggested that head and neck malignancies can occur at any age, with no differences across age groups.[13] Regarding the variable of anemia, the presence of a history of anemia (17.3%) was smaller compared to the group with no history of anemia (82.7%), which is consistent with other research indicating that 10.1% of patients receiving chemotherapy experience anemia.[14]

The incidence rates of nephrotoxicity, leukopenia, and anemia are higher with cisplatin administration, whereas carboplatin administration is associated with a higher incidence of thrombocytopenia.[15] Many derivatives of cisplatin have been developed, such as carboplatin, oxaliplatin, nedaplatin, hepteplatin, and

lobaplatin, but none have surpassed cisplatin in terms of effectiveness and spectrum of action.[16] Subjects in this study mostly received cisplatin regimen (87.7%) compared to carboplatin therapy regimen (12.3%), which is because cisplatin is recognized as the first-line therapy for head and neck malignancies and is considered the most effective neoadjuvant or concomitant therapy with radiotherapy.[17]

One of the common complications after chemotherapy is the decline in hearing function, which is one of the effects of chemotherapy-induced ototoxicity. Research indicates that platinum-based chemotherapy, both cisplatin and carboplatin, is the leading cause of ototoxicity compared to other chemotherapy drugs. Although carboplatin has similar anti-tumor effects as cisplatin, it has milder ototoxic effects. Studies have reported ototoxicity rates ranging from 45–83.3% for cisplatin and varying from 16.6–75% for carboplatin.[18] Another study on decreased bone conduction in nasopharyngeal carcinoma post-platinum-based chemotherapy found that 53% of the cisplatin group experienced decreased bone conduction, and 42.3% in the carboplatin group.[19]

The results of this study indicate that the cumulative dose of platinum-based chemotherapy drugs, both cisplatin and carboplatin, is significantly associated with the occurrence of chemotherapy-induced ototoxicity (p=0.001), with a moderate correlation between cumulative dose and ototoxicity (r=0.404). Consistent with previous research, hearing impairment occurs in 26% of patients at cumulative cisplatin doses between 300–600 mg/m^2, and around 12% at doses <200 mg/m^2.[5] This study found that ototoxicity appears (4%) after the first cycle of cisplatin regimen, indicating that ototoxicity begins to occur after receiving a chemotherapy dose of 80mg/m^2. This aligns with previous research indicating that high-frequency hearing impairment can occur with individual cisplatin doses exceeding 60 mg/m^2.[2,20]

Gender, age, and history of anemia are confounding factors in this study, so bivariate analysis was conducted on gender, age, and history of anemia to determine their relationship with chemotherapy-induced ototoxicity. The analysis revealed no relationship between gender, age, and history of anemia with chemotherapy-induced ototoxicity. This is consistent with previous research indicating that gender does not influence chemotherapy drug toxicity.[21] Other researchers have suggested that advanced age (>65 years) does not affect the incidence and severity of chemotherapy drug toxicity compared to younger ages.[22,23] However, contrary findings suggest that advanced age and low hemoglobin levels are associated with platinum-based chemotherapy-induced ototoxicity.[24]

CONCLUSION

There is a moderate positive relationship between cumulative dose of platinum-based chemotherapy and the occurrence of ototoxicity in head and neck malignancies. Confounding factors such as gender, age, and history of anemia do not affect the occurrence of ototoxicity in this study.

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Original Article

Risk Factors for Peripheral Vertigo

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Abstract

Background : Several risk factors influence the occurrence of peripheral vertigo, including advanced age, gender, and chronic metabolic diseases. This disease is not widely recorded in primary care due to the need for detection with simple examinations. Research on the association of several risk factors has yet to be reported. The objectives of this study was to examine the relationship between age, gender, type 2 diabetes mellitus (DM2), and hypertension as risk factors for peripheral vertigo.
Methods : This study is a case-control study that used consecutive sampling. The study sample consisted of 39 people: 19 in the case group and 20 in the control group. Data were obtained from 2 health centers and Diponegoro National Hospital, Semarang City. The data were obtained from history taking and physical examinations such as the Gans Sensory Organization Performance Test (SOP), past pointing test, and dysdiadokokinesia test. DM2 disease and hypertension were gathered from medical records. Data analysis used univariate analysis, bivariate analysis with chi-square, and logistic regression multivariate analysis.
Results : Statistical test results concluded that hypertension is a risk factor for peripheral vertigo (p = 0.008; OR = 6.964; 95%CI = 1.657 – 29.263). Whereas age, gender, and DM2 were not risk factors, with p-values of 0.187, 0.378, and 0.417, respectively.
Conclusion : The significant risk factor associated with the occurrence of peripheral vertigo was hypertension by 6.964 times.

Keywords : Peripheral vertigo, risk factors, hypertension

INTRODUCTION

Vertigo is a symptom of dizziness with a spinning head as if there is a rotating motion of the patient towards the surroundings or the surrounding environment that rotates towards the patient.[1] Peripheral vertigo can occur due to disorders in the inner ear organs, including the vestibular nerve. The inner ear organs involved in the balance system can be the semicircular canal, utriculus, or saculus.[2]

Symptoms of vertigo significantly affect comfort, quality of life in the organ system, emotional stability, and social environment at work.[3] Patients with mild vertigo sometimes do not immediately seek health treatment. However, severe symptoms cause patients not to dare to move, causing patients to immediately seek treatment either at the hospital or the health center. This condition is an emergency because the risk of falling is more significant, especially in the elderly. Although it is only a symptom, the causative factors or risk factors need to be sought to optimize management to prevent recurrence.[4]

Symptoms of vertigo need to be sought in detail from the history to determine the type of vertigo involving the inner ear, which is then clarified by the results of physical examination both in general and localized to the ear. This is to rule out the possibility of differential diagnosis of central vertigo.[5] Evaluation of vestibular system function can be done with some simple balance physical examination in primary health facilities without special equipment.[2] The Gans Sensory Organization Performance Test (SOP) is a simple physical examination to assess the function of the body's balance system. It is a simple examination which is readily available, is safe for patients and can be done at primary health care.[6]

The incidence of peripheral vertigo is estimated from 3% to 10% of the population.[7] Research on the prevalence of vertigo in Indonesia has yet to be recorded accurately. This number may increase with age and is influenced by gender. Chronic metabolic diseases such as type 2 diabetes mellitus (DM2) and hypertension are suspected to affect the occurrence of peripheral vertigo.[8] The prevalence of vertigo among elderly ranges from 33–35%.[3] The elderly with hypertension experience more peripheral vertigo than those without hypertension (23.8%; 16%).[1] The incidence of BPPV with DM2 disease is more significant than BPPV alone.[8]

Age and female have been reported as risk factors for vertigo or dizziness.[9] Systemic metabolic disorders such as DM and hypertension are risk factors for the vestibular system.[8,10] Patients with thick blood and heart disease may experience dizziness triggered by head movement. This condition involves blood circulation disorders due to decreased oxygen concentration, which affects tissue perfusion, mainly in peripheral areas with tiny blood vessels, such as the ear's vestibular organs.[3]

RESEARCH METHODS

This study is an observational analytic with a case-control design conducted from November 2021 to April 2022. The selection of research subjects was carried out using a consecutive sampling method. The inclusion criteria of the case group were patients with peripheral vertigo aged ≥26 years and willing to participate.

Subjects were selected from patients of Ngesrep Health Center, Kagok Health Center, and Diponegoro National Hospital in Semarang City. Subjects were explained the study's purpose, objectives, benefits, and procedures and then filled out informed consent. Diagnosis of peripheral vertigo was done by taking anamnesis related to vertigo symptoms (description, duration, onset, and precipitating factors). Patients were examined using the Gans Sensory Organization Performance Test (SOP), as well as dysmetria and dysdiadokinesia examinations. The tools used were the respondent form and foam for the Gans Sensory Organization Performance Test.

The risk factor data of this study were age, gender, DM2, and hypertension. These variables were nominal scale. Age was categorized into ≥50 years and <50 years. Diagnoses of DM2 and hypertension were from medical records.

The collected data were analyzed using univariate, bivariate, and multivariate analyses using SPSS version 26 IBM statistical software. Bivariate analysis was performed using the Chi-Square test or Fisher's test to determine the relative risk by calculating the odds ratio. Multivariate analysis was performed with logistic regression using the backward stepwise method.

This study has obtained ethical permission from the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University Semarang.

RESEARCH RESULTS

This study involved 39 subjects: 19 in the case group and 20 in the control group. The youngest of the study subjects was 40 in the control group, and the oldest was 83 in the case group. Subjects with DM2 and hypertension who experienced peripheral vertigo accounted for 62.5%. Table 1 shows the characteristics of the study subjects.

In Table 2, it was found that hypertension caused peripheral vertigo significantly and by 6.964 times ($p = 0.015$; OR = 6.964; 95%CI = 1.657 - 29.263). Age was not a risk factor for peripheral vertigo ($p = 0.187$). The female gender in the case group was more than male, with a percentage of 84.2% and 15.8% ($p = 0.378$). In this study, DM2 was also not a risk factor for peripheral vertigo ($p = 0.417$).

The results of multivariate logistic regression showed that hypertension was the most significant risk factor for peripheral vertigo ($p = 0.008$). They caused peripheral vertigo by 6.964 times (Table 3).

DISCUSSION

Statistical results prove that hypertension was a significant risk factor for peripheral vertigo. Subjects with hypertension had 6.964 times the risk of peripheral vertigo. The results of this study were in line with previous studies which stated that hypertension was a risk factor for peripheral vertigo. The frequency of vertigo in the elderly with hypertension was higher than in healthy elderly, 23.8% and 16%,

TABLE 1
Characteristics of Research Subjects

Group		Case n (%)	Control n (%)	Total n (%)
Total	Male	19 (48.7)	20 (51.3)	39 (100)
Age	≥50 Years	18 (52.9)	16 (47.1)	34 (100)
	<50 Years	1 (20)	4 (80)	5 (100)
Gender	Female	16 (51.6)	15 (48.4)	31 (100)
	Male	3 (37.5)	5 (62.5)	8 (100)
DM2	DM2	7 (63.6)	4 (36.4)	11 (100)
	Not DM2	12 (42.9)	16 (57.1)	28 (100)
Hypertension	Hypertension	15 (68.2)	7 (31.8)	22 (100)
	Not Hypertension	4 (23.5)	13 (76.5)	17 (100)
DM2 and Hypertension		5 (62.5)	3 (37.5)	8 (100)

TABLE 2
Results of bivariate analysis

Category		Case n (%), n=19	Control n (%), n=20	*p-value*	OR	95% CI Lower	95% CI Upper
Age	≥50 years	18 (94.7)	16 (80)	0.187[a]	4.5	0.455	44.546
	<50 years	1 (5.3)	4 (20)				
Gender	Female	16 (84.2)	15 (75)	0.378[a]	1.778	0.361	8.764
	Male	3 (15.8)	5 (25)				
DM2	Yes	7 (36.8)	4 (20)	0.417[b]	2.333	0.554	9.834
	No	12 (63.2)	16 (80)				
Hypertension	Yes	15 (78.9)	7 (35)	0.015[b*]	6.964	1.657	29.263
	No	4 (21.1)	13 (65)				

Note: *significant if *p-value* <0.05, [a] Fisher's exact test, [b] Chi-Square test

respectively.[1] Hypertensive patients had a risk of 1.51 times the recurrence of peripheral vertigo compared to people without hypertension.[11]

Hypertension as a chronic vascular disease can increase the incidence of atherosclerosis and thicken blood vessel walls, which leads to decreased oxygen and nutrient perfusion in the vestibular system both centrally and peripherally.[1,12] Decreased tissue perfusion will trigger impaired function of hair cell receptors in the peripheral vestibular system. Previous studies have shown that there was a significant difference in the prevalence of vestibular system function disorders in patients with hypertension.[13] Hypertension also increases the risk of otoconia fragment release in the endolymph fluid, which can cause BPPV.[13,14] The most common peripheral vertigo disease from all cases was BPPV, so hypertension can be a risk factor for peripheral vertigo.[3]

The results of the analysis in this study concluded that age was not a risk factor for peripheral vertigo. Previous studies on peripheral vertigo patients were more about age more than 50 years ($p \leq 0.005$) and estimated to have a risk of 1.8 times compared to respondents with younger age.[7] The age distribution in both groups was not balanced, so it was a weakness in this study because of the limited research time to find patients with peripheral vertigo. However, in this study, peripheral vertigo was more common in the elderly.

Comorbid diseases in the elderly can be a risk factor for peripheral vertigo, although, in some studies, it was still not proven. A study showed that people with DM2 with hypertension would be at risk of BPPV compared to people

TABLE 3
Logistic regression test results

Variable		*p-value*	Exp(B)	95% CI	
				Lower	Upper
Step 1	Age Category	0.482	2.439	0.455	44.546
	Hypertension	0.015	6.134		
Step 2	Hypertension	0.008*	6.964	0.361	8.764

Notes: *significant if *p-value* <0.05

with DM2 without hypertension 8 This was also supported by previous research with the results of all respondents who experienced recurrent BPPV. As many as 123 (22.3%) respondents had one comorbid disease, which increased to 255 (46.3%) respondents with more than one comorbid disease.[14] Physical activity and mobilization of respondents were allegedly able to affect balance ability, but the study was not analyzed. Physical activity was said to prevent BPPV in the elderly.[15] A decrease in physical activity and mobilization in the elderly will increase the risk of recurrent BPPV.[16]

Gender can be a risk factor for peripheral vertigo. Previous studies have shown that women were more at risk of peripheral vertigo than men, with a difference in the proportion of respondents, 768(71.3%) women and 309 (28.7%) men, and increased the risk by 4.4 times in women.[7] However, in this study, gender was not a statistical risk factor. Menopausal factors may influence the results of this analysis. Women who have menopause will experience a decrease in estradiol hormone, which plays a role in preventing microcirculation damage to the KSS and maintenance of otoconia. Damage to microcirculation in the KSS and decreased expression of proterin in otoconia can cause otoconia dislocation, which triggers BPPV. A study showed that BPPV patients had lower estradiol levels than non-BPPV patients ($p < 0.001$).[17] Another study reported that although the proportion of women experiencing BPPV was higher than men, 62.7% to 37.3% of 1092 respondents, only 48.8% of women experienced BPPV recurrence, while 53.3% of men experienced a recurrence of all cases.[14]

DM2 was significantly associated with the incidence of BPPV.[8] Different results reported in a systematic review and meta-analysis journal suggested by twelve journals and 10,869 respondents showed DM disease did not cause the incidence of BPPV (p=0.71).[18] But in this study, it was not proven significantly to be a risk factor for peripheral vertigo (p=0.4178).

The duration of DM2 may affect the results of the analysis. The duration of DM affects the progression of microvascular complications, including vestibular system dysfunction. The results of multivariate analysis from previous studies showed that the duration of DM of more than ten years was a risk factor for several microvascular complications, with more than 50% experiencing microvascular complications after 12–14 years since first diagnosed.[19]

The limitation of this study was that other factors were not examined in detail, such as other comorbid diseases experienced by respondents, physical activity levels, menopausal status, duration of DM, and objective measurement of risk factors. This study did not use a matching method to reduce research bias. This study only detected peripheral vertigo and has not been categorized.

CONCLUSION

Hypertension was a risk factor for peripheral vertigo by 6.964 times. However, advanced age, female gender, and DM2 in this study were not proven to be risk factors for peripheral vertigo.

The researcher suggested further research that recorded risk factors for peripheral vertigo, such as other comorbid diseases, physical activity level, menopausal status, duration of diabetes, and objective measurement of risk factors. Further research with the same independent variables, a larger sample size, and matching in the respondent group was needed to reduce research bias. It is also necessary to conduct similar research on more specific types of peripheral vertigo.

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Original Article

The Effect of Cold Temperature on the Severity of Allergic Rhinitis Based on Visual Analog Scale (VAS) Score among Medical Students of Malikussaleh University

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Abstract

Background : Allergic rhinitis is a common condition caused by inflammation of the nasal mucosa after exposure to allergens and is mediated by Immunoglobulin E (IgE). Cold temperatures can aggravate the symptoms of allergic rhinitis. Allergic rhinitis is not fatal, but it can cause a decrease in the patient's quality of life if the symptoms are severe. The severity of allergic rhinitis symptoms is difficult to measure as it should match patient's perception, so VAS is a quantitative measurement tool used. Although VAS is a simple and easy-to-use tool, its use as self-monitoring for AR patients is still infrequent to minimize symptom exacerbations and maintain control of allergic rhinitis. This study aims to examine the effect of cold temperature on the severity of allergic rhinitis based on VAS score.

Methods : This research is an experimental with a one-group pretest-posttest study. The study samples involved 75 students suffering from allergic rhinitis assessed with the Score for Allergic Rhinitis (SFAR) questionnaire assessment from the class of 2020, 2021, and 2022. Subjects' pain level was measured before and after the intervention. The intervention was in the form of cold temperature exposure for 15 minutes in a room with a temperature of 18°. Data were analyzed using the Wilcoxon test.

Results : The results showed that the mean VAS score before the intervention was 0 while after the intervention was 38.61 ± 24.07. This shows that the mean VAS score after the intervention is higher than the mean VAS score before the intervention (*p-value* = 0.00 <0.05).

Conclusion : The results of this study indicate that the effect of cold temperature can increase the severity of allergic rhinitis.

Keywords : allergic rhinitis, SFAR, cold temperature, VAS

INTRODUCTION

Allergic rhinitis is an inflammatory condition of the nasal mucosal lining caused by an Immunoglobulin E (IgE)-mediated allergic reaction to an allergen. Symptoms include sneezing, rhinorrhea, itchy nose, and nasal congestion. These symptoms can spread to other organs, such as the eyes, skin, and lungs. Allergic rhinitis can be classified based on the duration of symptoms (intermittent and persistent) and severity (mild, asymptomatic, and moderate-severe). Intermittent is symptoms that occur ≤4 days per week or last ≤4 weeks. While persistent symptoms that appear >4 days per week and last >4 weeks. Allergic rhinitis symptoms can interfere with daily activities and have an impact on socioeconomic aspects.[1]

The prevalence of allergic rhinitis (AR) in the world ranges from 10–20%, while in Indonesia it ranges from 1.5–12.4%. This figure is quite high, although AR does not cause death, it can affect a person's quality of life. Aceh province has the highest prevalence of 49.8% and North Sumatra province has the lowest prevalence of 5.9%. However, for Lhokseumawe City there is no data on the prevalence of RA. The prevalence of allergic rhinitis in the last 10 years has increased worldwide, including Indonesia. Genetic and environmental factors are the cause. The prevalence of allergic rhinitis also varies from country to country, influenced by geographical factors and potential aeroallergens. Several other factors such as air temperature, occupation, environment, exposure to cigarette smoke, and previous history of allergy, can aggravate symptoms.[2]

Cold air can be a triggering factor for allergic rhinitis.[3] In cold temperatures, exposure to allergens increases due to elevated dust and contaminant levels, poor ventilation, changing temperatures, and dry air. This can lead to irritation and hypersensitivity of the nasal mucosa, increasing the risk of allergies.[4] Cold temperatures can cause functional impairment in individuals with respiratory diseases. This is because cold temperatures can cause hyperresponsiveness and constriction of the respiratory airways. In addition, cold temperatures can also worsen complaints in individuals who have chronic respiratory diseases.[5] Air conditioners (ACs) cool, dry, clean, and circulate the air. However, air conditioners that are too cold and dry can trigger symptoms of allergic rhinitis, such as runny nose, sneezing, and nasal congestion.[6] Research conducted by Yogeetha R., *et al* in 2007 which examined the "Effects of temperature changes on nasal patency" showed that when exposed to air conditioning temperatures with a temperature of 18° for 15 minutes the nose tends to experience increased nasal resistance compared to normal room temperature air.[7]

The symptoms of allergic rhinitis are subjective and should match the perception of the patient. Signs and symptoms of AR can vary from individual to individual. Therefore, it is very difficult to measure the severity of allergic rhinitis. Visual Analog Scale (VAS) is a quantitative measurement tool used to assess the severity of AR symptoms. Several studies have shown that VAS can be used to assess AR symptoms and assess the quality of life of patients. Visual Analog Scale (VAS) is a simple and easy-to-use tool that is effective for measuring disease severity and objectifying symptoms and can monitor the development of allergic rhinitis in patients. VAS can also be used to evaluate the level of disease control. The VAS consists of a 100 mm horizontal line, with the left end representing no symptoms and the right end representing the most severe symptoms. Higher VAS scores indicate greater intensity of the symptoms they feel. Although its application is simple and effective in assessing AR symptoms, its use as self-monitoring is still very rare using VAS to minimize symptom exacerbation and maintain allergic rhinitis control.[8]

Therefore, researchers are interested in conducting further research to examine the effect of cold temperature on the severity of allergic rhinitis using VAS assessment in students of the Malikussaleh University Medical Study Program.

METHODS

This study is an experimental study with a one-group pretest-posttest. The study was conducted at the Faculty of Medicine, Malikussaleh University, Lhokseumawe, Indonesia, on August 27 – September 18, 2023. This research was conducted for 23 days. The study population was students of the Malikussaleh University Medical Study Program class of 2020, 2021, and 2022. The sample was selected using a total purposive sampling technique, namely respondents who met the inclusion and exclusion criteria. The inclusion criteria of this study were students of the Malikussaleh University Medical Study Program class of 2020, 2021, and 2022, students who suffered from allergic rhinitis based on the results of initial screening using the Score For Allergic Rhinitis (SFAR) questionnaire, willing to become research subjects by filling out informed consent and questionnaires completely, and not using drugs for at least 7 days that could affect the results of the study during the study period (antihistamines, corticosteroids, decongestants, and herbal medicines). Meanwhile, the exclusion criteria in this study were students who had a history of asthma. After using the total purposive sampling technique, the total number of respondents was 75 people. The independent variable of this study was cold temperature. The dependent variable was the severity of allergic rhinitis. Cold temperature was measured using a Samsung brand 1 PK air conditioner and calibrated with a Notale brand room thermometer with model number NTL-HM370. The temperature was

set at 18° in a 3 x 4 room. All research samples were divided into 19 sessions. In 1 session, 4 research samples were given cold temperature intervention for 15 minutes in the room. The severity of allergic rhinitis was measured using a Visual Analog Scale (VAS) score that has a horizontal line of 100 mm. The higher the score given on the VAS sheet, the more severe the AR symptoms experienced by the sufferer. Scores <20 mm are categorized as well-controlled AR, scores of 20 – 50 mm are categorized as partially controlled AR, and scores >50 mm are categorized as uncontrolled AR. Before and after the cold temperature intervention, the research sample was given a VAS sheet to assess the severity of AR symptoms they felt and what symptoms had worsened after the cold temperature intervention. Data processing and analysis were carried out using the Wilcoxon test with a significance value set at p <0.05. Wilcoxon test was used to see the effect of cold temperature on the severity of allergic rhinitis based on VAS score. The Research was approved by Health Research Ethics Committe of Faculty of Medicine Malikussaleh University Lhokseumawe.

RESULTS

Based on the screening results, 75 people met the criteria for allergic rhinitis with SFAR ≥7. Of these, 53 samples (70.7%) were female and 22 samples (29.3%) were male. This proportion was obtained by total purposive sampling technique, which is a sampling technique with certain considerations and all samples that meet the inclusion and exclusion criteria.

The results of this study showed that some AR symptoms in the study sample worsened after cold temperature intervention (Table 1). Whereas before the cold temperature intervention, all research samples did not experience worsening AR symptoms.

Based on the table above, it can be concluded that several symptoms of AR can appear simultaneously in samples after cold temperature intervention. The most common symptoms of allergic rhinitis complained by the study samples were sneezing as many as 42 samples, rhinorrhea as many as 34 samples, itchy nose as many as 22 samples, watery eyes as many as 17 samples, nasal congestion as many as 10 samples, asymptomatic as many as 8 samples, itchy eyes as many as 4 samples, and reddish eyes as many as 3 samples. The well-controlled allergic rhinitis category includes 3 symptoms listed in the table, including rhinorrhea, sneezing, and nasal congestion. The partially controlled AR category includes 5 symptoms listed in the table, including sneezing, rhinorrhea, itchy nose, nasal congestion, and watery eyes. While in the uncontrolled AR category, symptoms such as sneezing, rhinorrhea, itchy nose, nasal congestion, watery eyes, itchy eyes, and eye redness can all occur.

Based on the VAS score assessment carried out by the research sample, the level of control of allergic rhinitis can be classified both before the intervention (pretest) and after the cold temperature intervention (posttest). The results of the study before the cold temperature intervention, all VAS score sheets filled out by the research samples showed a score of 0, so all research samples were classified into the category of well-controlled AR. While the level of AR control varies after cold temperature intervenes (Table 2).

Based on the Table 2, it can be concluded that before the cold temperature intervention, all research samples (100%) had a mean ± SD of 0 based on the VAS score. This is because all samples have a value of 0 on their VAS score. The research sample also did not show any worsening of AR symptoms. Meanwhile, after the cold temperature intervention at 18° for 15 minutes, most of the research samples showed an increase in VAS scores. There is a difference in individual values, with mean ± SD of 38.61 ± 24.07. This indicates that there is an exacerbation of allergic rhinitis symptoms experienced by the research sample, as evidenced by an increase in the

TABLE 1
Worsening of AR Symptoms in Research Samples After Cold Temperature Intervention

Symptoms AR	Control Level of Allergic Rhinitis (AR)		
	Well controlled	Partially controlled	Not controlled
Asymptomatic	8	–	–
Sneezing	2	21	19
Rhinorrhea	3	20	11
Itchy nose	–	14	8
Nasal congestion	1	2	7
Watery eyes	–	4	13
Itchy eyes	–	–	4
Eye redness	–	–	3

TABLE 2
AR Control Level After Cold Temperature Intervention (n=75)

Control Level of Allergic Rhinitis		
Well controlled (<20 mm)	**Partially controlled (20 – 50 mm)**	**Not controlled (>50 mm)**
15	37	23

TABLE 3
Analysis of Differences in VAS Scores Before (Pretest) and After Cold Temperature Intervention (Posttest)

Group	Median	Min	Max	X ± SD	*p-value*
Pretest	0	0	0	0	0.000
Posttest	33	0	80	38.61 ± 24.07	

mean VAS score before and after the cold temperature intervention.

The results of the analysis using the Wilcoxon test also showed that there was a significant difference between the pretest and posttest results on the VAS score of Malikussaleh University Medical Study Program students. This is known from the *p-value* = 0.000 <0.05. Thus, the research hypothesis (Ha) is accepted in this study and it can be concluded that cold temperature affects the severity of allergic rhinitis based on Visual Analog Scale (VAS) scores in Malikussaleh University Medical Study Program students.

DISCUSSION

The results of this study suggest that cold temperature intervention can lead to an increase in the severity of allergic rhinitis. Air temperature can affect respiratory function directly or indirectly. Cold air can trigger an allergic rhinitis attack by increasing airway hyperresponsiveness which causes narrowing of the respiratory tract. This finding is in line with previous studies showing that exposure to cold temperatures can trigger allergic reactions, worsen allergic rhinitis symptoms, and increase the risk of impaired respiratory function in individuals with allergic rhinitis. The increased severity of allergic rhinitis symptoms due to cold temperatures can be caused by several factors, including increased resistance and decreased nasal patency, water loss that occurs during cold temperature exposure, as well as nasal mast cell activation, and sensory nerve stimulation that can trigger cholinergic reflexes, causing rhinorrhea.[9]

Based on the Central Board of the Indonesian Ear Nose Throat Head Neck Surgery Specialist Association in 2016, cold and dry air can be a triggering factor for allergic reactions, regardless of the type of allergen.[10] Cold air can cause blood vessels in the nasal mucosa to dilate (vasodilation), resulting in decreased airflow in the nose and increased nasal resistance. This can cause respiratory distress, especially nasal congestion.[11] In addition, allergic rhinitis symptoms can also be caused by the nervous system. An imbalance between the parasympathetic and sympathetic nervous systems can cause the blood vessels in the nose to become more permeable and the mucus glands under the nasal mucosa layer to produce more mucus. This can lead to symptoms of rhinorrhea and nasal congestion.[12] Symptoms of allergic rhinitis can also involve the eyes, with itching, watering, or redness. The pathological mechanism involves type-I hypersensitivity mediated by IgE.[13]

Besides the cold temperature factors, other factors can affect the symptoms of allergic rhinitis, one of which is gender. Based on the results of research on the prevalence of allergic rhinitis, women are higher than men. This is supported by research by Utama in 2010 and Rafi in 2015 which found that women experience more allergic rhinitis. Rambe's research in 2013 explained that this can occur because women and men have different perceptions of pain. Women may be more sensitive to pain so they seek medical attention more often. However, the prevalence of allergic rhinitis in children, boys experience allergic rhinitis more often than girls. However, after adulthood, allergic rhinitis is higher in women than men. This is due to hormones such as estrogen and progesterone which play an important role in women's tendency to develop allergic diseases. These hormones support allergic responses such as Th2 polarization, trigger degranulation of mast cells and basophils, and increase Th2 cell production.[14]

The level of allergic rhinitis control can be determined through VAS scores. VAS score >50 mm indicates uncontrolled AR, VAS 20 – 50 mm indicates partially controlled AR, and VAS < 20 mm indicates well-controlled AR.[15] The degree of control of allergic rhinitis is proportional to its severity. The more severe the allergic rhinitis, the less controlled it will be. A well-controlled allergic rhinitis is a condition where the patient does not experience symptoms or the symptoms do not interfere with daily activities. While partially controlled or uncontrolled allergic rhinitis is a condition that makes patients experience symptoms that interfere with daily activities.[16] The varying degree of control of allergic rhinitis is due to the individual's response to cold temperatures which can also vary, thus affecting whether or not symptoms appear during the intervention. In general, allergic rhinitis symptoms are caused by environmental factors, such as exposure to allergens, one of which is due to exposure to cold temperatures, and internal factors such as excessive immune response.[17] Therefore, people with allergic rhinitis need to understand the condition of the disease to recognize signs of exacerbation and take preventive measures.[18]

AR symptoms may result from a second-phase allergic reaction. Second-phase allergic reactions occur when allergens bind to IgE bound to mast cells and basophils. This causes mast cells and basophils to release chemicals, such as histamine, prostaglandins, leukotrienes, bradykinin, and Platelet Enacting Figure (PAF). These chemicals cause inflammation of the nasal mucosa, resulting in symptoms of allergic rhinitis, such as sneezing, itchy nose, nasal congestion, and rhinorrhea.[19] Late-phase reactions are inflammatory responses that occur after allergen exposure. This reaction can prolong the symptoms of allergic rhinitis and increase the risk of future exacerbation of symptoms. Cytokines and chemokines released during late-phase reactions can lead to further release of inflammatory mediators and will worsen allergic rhinitis symptoms.[20]

Normally, in people with allergic rhinitis, repeated exposure to allergens causes the immune system to produce specific IgE antibodies against those allergens. When the sensitizing allergen binds to IgE antibodies bound to cells, the cells release chemical mediators such as histamine, leukotrienes, prostaglandins, and kinins. These chemical mediators cause immediate hypersensitivity in the form of itching in the nose, eyes, and throat, sneezing, and nasal congestion.[20]

CONCLUSION

This study concludes that exposure to cold temperatures can increase the severity of allergic rhinitis symptoms based on VAS scores. Assessment using the VAS score is expected to be a self-monitoring for allergic rhinitis patients to minimize symptom exacerbation and maintain allergic rhinitis control.

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Original Article

Significant Relationship between Brixia Score and The Degree of Acute Respiratory Distress Syndrome in Covid 19 Patients

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Abstract

Background : Chest X-ray has an important role in detecting early features of COVID-19. To improve risk stratification, a scoring system in chest x-ray called Brixia Score was developed. The Brixia score is designed to measure the severity of lung abnormalities in COVID-19, with an 18-point severity scale. Deaths in COVID-19 occur mainly due to Acute Respiratory Distress Syndrome (ARDS). ARDS is classified into mild, moderate, and severe degrees. If the degree can be predicted earlier, patients can receive earlier therapy and death rate can be reduced. This study was aimed to analyze relationship between Brixia Score and degree of ARDS in COVID-19 patients.
Methods : the research used an observational analytic method with a cross-sectional approach to 95 subjects who are positive for COVID-19 and diagnosed with ARDS, in January to December 2021. Brixia Score data was collected based on chest X-ray expertise, ARDS degree was based on medical records and blood gas analysis. Analysis of relationship between Brixia score and degree of ARDS was carried out using the Kruskal-Wallis test.
Results : There was a significant difference in Brixia score based on degree of ARDS (*p-value* <0.05). The highest Brixia score was obtained in severe ARDS, while the low Brixia score was obtained in mild ARDS. This proves that there is a relationship between Brixia score and degree of ARDS.
Conclusion : Brixia score has a significant relationship to the degree of ARDS in COVID-19 patients.

Keywords : ARDS, Brixia Score, COVID-19, degree of AR

INTRODUCTION

COVID-19 (*Coronavirus disease* 2019) is an infectious disease caused by the *severe acute respiratory syndrome coronavirus-2* (SARS-CoV-2 virus). The COVID-19 diagnosis is established based on the combination of medical history, contact tracing, physical examination, laboratory examination, radiology examination, and a definitive diagnosis by conducting a *reverse transcriptase polymerase chain reaction* (RT-PCR) test to obtain its result. The chest X-ray and the chest *computed tomography* (CT) scan play crucial roles in the COVID-19 diagnosis, as a modality to detect the imaging features of early COVID-19. In this way, it helps the physician determine the diagnosis before the RT-PCR result is ready.[1–6]

In order to improve risk stratification and help physicians determine the needs of high-risk patients, a chest X-ray scoring system for the COVID-19 lesion has been developed. It is known as the Brixia Score. This is a semi-quantitative scoring system that is designed to measure the degree of lung disease severity in COVID-19, in which the role of the lung is scored on an 18-point severity scale based on the total width and the disorder characteristic of the lungs. [7–11]

Deaths in COVID-19 are mainly caused by *acute respiratory distress syndrome* (ARDS). Based on the ratio of *partial pressure arterial oxygen* (PaO_2) divided by the *fraction of inspired oxygen* (FiO_2), the ARDS is classified into the stages of mild, moderate, and severe. A patient who develops the ARDS is at a higher risk of 45% death rate. When the stages of ARDS are detected earlier, it is expected that a patient will undergo faster and more precise therapy. Furthermore, prognosis improvement can be made to meet the reduction in mortality rate.[12–16]

This research aims to investigate the relationship between the Brixia Score and the stages of ARDS in COVID-19 patients.

METHODOLOGY

This research has been declared as ethically appropriate by the Health Research Ethical Committee (KEPK) of Dr. Kariadi Central General Hospital (RSUP) Semarang.

This research applied the observational analytic method with a retrospective cross-sectional study on 95 research subjects who had been confirmed positive for COVID-19 and had been hospitalized from January to December 2021 and diagnosed with ARDS. The inclusion criteria are as follows: a) the patients who were positive for COVID-19 and had been examined with RT-PCR; b) the chest X-ray examinations and the Brixia score calculations were done on the first day when the patients were hospitalized; c) blood gas analysis were done on the first day when the patients were hospitalized and the ratio of the PaO_2/FiO_2 less than or equal to 300 mmHg; c) during the X-ray processes and blood gas tests, the patients had not received mechanical ventilation assistance; d) The patients' data had been stated in the medical records. The exclusion criteria are patients with congestive heart failure, pleural effusion, severe lung disease history, and tuberculosis.

The research subjects' data were collected from the medical records, chest X-ray examination data, and the radiologist expertise of the patients' chest X-rays. The following step was to make inclusion and exclusion based on the defined criteria. The data that had been obtained was secondary. Next, the analysis of the relationship between the Brixia Score and the stages of the ARDS was conducted with the Kruskal-Wallis test.

RESULTS

This research included 95 research subjects, consisting of 60 males (63.2%) and 35 females (36.8%). The mean of the subjects' ages is 57.31, with the youngest at 22 years old and the oldest at 83 years old, and the median is 58 years old. The treatments resulted in 56 recovered subjects (59%) and 39 dead subjects (41%). Out of 95 subjects, there are 23 subjects (24.2%) with hypertension as the comorbidity, and 46 subjects (48.4%) with diabetes mellitus as the comorbidity (Figure 1).

Based on the chest X-ray evaluations on the first day the subjects were hospitalized, the average number of Brixia Score is 9.6 out of the 95 research subjects, with the median of the Brixia Score at 10 (Table 1). Furthermore, this research found that there are subjects with Brixia score at 0 and marked it as the minimum score, and there are subjects with Brixia score at 18 and marked it as the maximum score. The analysis of the chest X-rays was aimed at finding lesion characteristics in the subjects. Nevertheless, it discovered 1 subject with a normal chest X-ray (1.05%) and 94 subjects with abnormalities on the chest X-rays (98.95%). These abnormalities consist of 85 subjects with bilateral lesion distributions (89.4%), 67 subjects with dominant interstitial infiltrate lesion patterns (71.2%), and the majority of subjects (86 subjects) with lesion zonation on the left lower lung fields (91%) (Table 2).

Based on the *ratio of partial pressure arterial oxygen to fraction of inspired oxygen* (PaO_2/FiO_2) calculation, the result obtained the mean value at 167.97, followed by the median value at 99.50, the minimum value at 29.50, and the maximum value at 284.69 (Table 3). The result shows that out of the 95 research subjects, there are 13 samples (13.7%) with mild ARDS, 26 samples (27.4%) with moderate ARDS, and 56 samples (58.9%) with severe ARDS (Table 4).

Table 5 shows the correlation test between the Brixia Score and the *ratio of partial pressure arterial oxygen to fraction of inspired oxygen* (PaO_2/FiO_2) resulted in a *p-value* equaling 0.015, which means that the p-value is less than 0.05 ($p < 0.05$) and the correlation coefficient equals -0.248

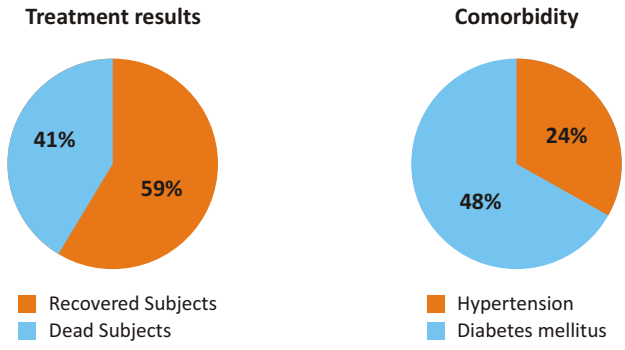

Figure 1. Treatment results and Comorbidities of the Subjects

TABLE 1
Brixia Score Descriptions of the Chest X-rays

Variable	Mean ± SD	Median (min – max)
Brixia Score	9.60 ± 5.61	10.00 (0–18)

TABLE 2
Lesion Characteristics on the Chest X-rays

Findings of the Chest X-rays		n; Percentage (%)
Lung images (n = 95)	Normal	1; (1.05%)
	Abnormal	94; (98.95%)
Distribution of lung lesions (n abnormal = 94)	Unilateral	9; (9.4%)
	Bilateral	85; (89.4%)
Zonation (n abnormal = 94)	Right upper lung fields	44; (46%)
	Left upper lung fields	38; (40%)
	Right middle lung fields	81; (86%)
	Left middle lung fields	78; (82.9%)
	Right lower lung fields	84; (89%)
	Left lower lung fields	86; (91%)
Lesion patterns (n abnormal = 94)	Dominant interstitial infiltrates	67; (71.2%)
	Dominant alveolar infiltrates	27; (28.7%)

(r = -0.248). These values show a significant negative relationship between the Brixia Score on the chest X-rays and the ratio of partial pressure arterial oxygen to the fraction of inspired oxygen.

Table 6 shows the result of the Kruskal-Wallis test shows a significant difference in the Brixia Score based on the stages of the ARDS, with a *p-value* less than 0.05 (p <0.05). The highest Brixia Score was obtained from the severe stage of the ARDS. On the other hand, the lowest Brixia Score was obtained from the mild stage of the ARDS. Accordingly, the results show scientific evidence of the relationship between the Brixia Score and the stages of the ARDS.

DISCUSSION

The results of this research show that out of the 95 research subjects, there are 13 samples (13.7%) with mild ARDS, 26 samples (27.4%) with moderate ARDS, and 56 samples (58.9%) with severe ARDS. This is in

TABLE 3
The Ratio of Partial Pressure Arterial Oxygen to the Fraction of Inspired Oxygen (PaO_2/FiO_2)

Variable	Mean ± SD	Median (min – max)
The ratio of PaO_2/FiO_2	167.97 ± 83.95	99.50 (29.5 – 284.69)

TABLE 4
Stages of the ARDS

The ratio of PaO_2/FiO_2	n; Percentage (%)	Description
300 mmHg ≥ X > 200 mmHg	13 (13.7%)	Mild ARDS
200 mmHg ≥ X > 100 mmHg	26 (27.4%)	Moderate ARDS
≤ 100 mmHg	56 (58.9%)	Severe ARDS

TABLE 5
The Correlation Test between the Brixia Score and the Ratio of Partial Pressure Arterial Oxygen to the Fraction of Inspired Oxygen (PaO_2/FiO_2)

Variable	Brixia Score		Description
	p	*R*	
The ratio of PaO_2/FiO_2	0.015	-0.248	Significant, negative

TABLE 6
Test of Difference between the Brixia Score and the Stages of the ARDS

Variable	Stages of the ARDS						*p-value* Kruskal -Wallis test)
	Mild (N=13)		Moderate (N=26)		Severe (N=56)		
	Mean	Median (Min–Max)	Mean	Median (Min–Max)	Mean	Median (Min–Max)	
Brixia Score	4.08 ± 4.6	1.00 (0–15)	7.92 ± 4.9	8.00 (1–18)	11.66 ± 5.0	12.00 (2–18)	< 0.05

Description: Statistical Method of the Kruskal–Wallis Te

accordance with the previous study by Gibson *et al*. (2020), in which the ARDS occurred in 42% of the COVID-19 patients, and around 81% of those patients would fall into the severe stage of the ARDS, and thus intensive care was recommended.[12,14,17]

Later, the result of the Spearman's rank correlation test shows a significant negative relationship between the Brixia Score and the ratio of partial pressure arterial oxygen to the fraction of inspired oxygen. The scientific evidence here shows that the higher the Brixia Score, the lower the ratio of partial pressure arterial oxygen to the fraction of inspired oxygen. This is in accordance with the previous study by Fogante *et al*. (2021), in which the findings showed that there is a relationship between the Brixia Score and the gas exchangeboth the increase and the declinein the alveoli, plus the severity of the pathological process inside the lungs.[12,18,19]

The following result of the Kruskal-Wallis test shows that there is a significant difference in the Brixia Score based on the stages of the ARDS. The highest Brixia Score was obtained from the severe stage of the ARDS, while the lowest Brixia Score was obtained from the mild stage of the ARDS. This is in accordance with the previous research by Zhichao Feng *et al*. (2020) by studying the CT-scan modality, thus finding that the high CT severity score is the independent risk factor for COVID-19 patients with the mild stage of the ARDS to develop into the severe stage of the ARDS. Research conducted by

Balbi *et al*. (2021) concluded that the Brixia Score is the independent predictive factor for deaths in COVID-19 patients. Furthermore, research conducted by Maroldi *et al*. (2020) found that the Brixia Score of the dead COVID-19 patients was higher than that of the recovered COVID-19 patients.[11,12,20,21]

This research has limitations that should be highlighted. This research does not conduct an analysis of the subjects who were positive for COVID-19 without ARDS. Also, this research does not investigate the relationship between the Brixia Score of the chest X-rays and the stages of the ARDS during the inpatient care of the subjects. Furthermore, this research does not study the subjects' comorbidities, which are probable to be the factor that would affect the research results.

CONCLUSION

This research shows the scientific evidence of the significant relationship between the Brixia Score and the stages of the *acute respiratory distress syndrome* (ARDS) in COVID-19 patients. Furthermore, these research results are expected to be a reference for physicians in determining the most accurate therapy for COVID-19 patients, specifically those who have high Brixia scores, so it would prevent complications and improve the prognosis.

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Original Article

Correlation Between Brixia Score Imaging and Clinical Laboratory Results in Severe-Critical Covid-19 Patients Receiving Standard Therapy Compared to Tocilizumab

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Abstract

Background : *Coronavirus infection disease 19* (COVID-19) is a global health issue. Brixia score and inflammatory markers can assess COVID-19 severity. Severe-critical phase becomes the main concern of clinicians in the management of COVID-19 to reduce mortality. Standard therapy for moderate to severe COVID-19 is convalescent plasma which functions as an antiviral and immunomodulator, while tocilizumab is an IL-6 antagonist which underlies the occurrence of cytokine storms in severe-critical COVID-19. This study was aimedto examine the correlation between the Brixia score and clinical laboratory results in patients with severe-critical degree of Covid-19 who received both standard therapy and tocilizumab

Methods : A retrospective cohort study of Brixia score, with clinical laboratory results of D-dimer, fibrinogen, ferritin, and CRP (C-reactive protein) COVID-19 patients with severe-critical phase who were administered standard therapy and tocilizumab who were treated at RSUP DR Kariadi Semarang, then a correlation was carried out between the Brixia score and clinical laboratory results using a correlation test Spearman.

Results : The research data consisted of 72 subjects divided into groups that were adiminstered tocilizumab therapy (36 subjects) and standard therapy (36 subjects). There was a significant correlation between the Brixia score and the D-dimer result with $p = 0.024$ ($p < 0.05$), correlation coefficient = 0.377 in the standard pre-therapy and post therapy. A *p-value* of less than 0.05 indicates no significant correlation between the Brixia score and clinical laboratory results before or after tocilizumab therapy.

Conclusion : There is a significant correlation between the Brixia score results and the D-dimer results in COVID-19 patients who are adiministered standard therapy, but not significant correlation in tocilizumab.

Keywords : COVID-19, Brixia score, tocilizumab, convalescent plasma

INTRODUCTION

World Health Organization (WHO) declared coronavirus infection disease 19 (COVID-19) as a public health emergency of international concern (PHEIC) due to a significant increase in confirmed cases in various countries. In Indonesia, the first case of COVID-19 was reported on March 2, 2020, in a woman who had close contact with the 24th confirmed case in Malaysia, while the second case was the mother of the first case. Over time, the number of confirmed COVID-19 cases in Indonesia reached 4,208,013 by July 2020, with 141,467 deaths.[1]

The diagnosis of COVID-19 is established based on a combination of medical history with contact tracing, physical examination, hematological examination, antigen swab test, real-time reverse transcriptase polymerase chain reaction (RT-PCR), and imaging. However, the definitive diagnosis still relies on RT-PCR results. Radiological imaging plays an important role in the diagnosis of COVID-19, although knowledge about this pneumonia is still evolving. Radiological imaging is used to detect early signs of pneumonia, assisting clinicians in making a diagnosis. It also provides insights into the severity, disease progression, and post-infection control.[4] The main imaging modalities used to detect COVID-19 are chest X-rays and computed tomography (CT) scans. Chest X-rays are less sensitive compared to CT scans, as approximately 40% of cases do not show abnormalities on X-rays. However, the American College of Radiology (ACR) does not recommend using CT as the first-line screening tool for diagnosing COVID-19.[5] CT scans are limited to symptomatic patients with specific clinical indications due to the challenges in infection control and prevention of cross-contamination. In chest X-rays of patients with COVID-19 pneumonia, findings such as ground-glass opacity (GGO), infiltrates, peribronchial thickening, focal consolidation, and other findings can be observed. A study conducted by Zubo Wu *et al* in 2021 found a significant correlation between the degree of pneumonia and thoracic radiological findings in severe-critical COVID-19 patients.[5–7]

Based on the pathogenesis of COVID-19, most deaths occur in the severe-critical phase. This phase is of primary concern to clinicians in the management of COVID-19 as it determines prognosis. Therefore, treatment modalities for COVID-19 in the severe-critical phase are crucial in reducing patient mortality.[14] The most effective measures to reduce the incidence of COVID-19 are early detection, source isolation, and supportive care for confirmed cases. According to the COVID-19 Management Guidelines (3rd edition) issued by five professional medical organizations in Indonesia, the treatment for asymptomatic, mild, and moderate cases of COVID-19 is clear. However, in severe-critical cases, if there is no improvement with standard treatment, there are four treatment modalities still under operational research and have varying success rates among different studies: tocilizumab, convalescent plasma, IVIG, and stem cells. Therefore, this study aims to examine the correlation between Brixia Score imaging and clinical laboratory results in severe-critical COVID-19 patients receiving standard therapy compared to tocilizumab, to predict patient morbidity and mortality during treatment.[13]

Considering the severity and clinical complexity of severe-critical COVID-19, some studies have also analyzed the combination of multiple treatment modalities, such as convalescent plasma and tocilizumab. Mathew conducted a systematic review, and Khamis conducted a cohort study. In the systematic review by Mathew, which included seven retrospective studies

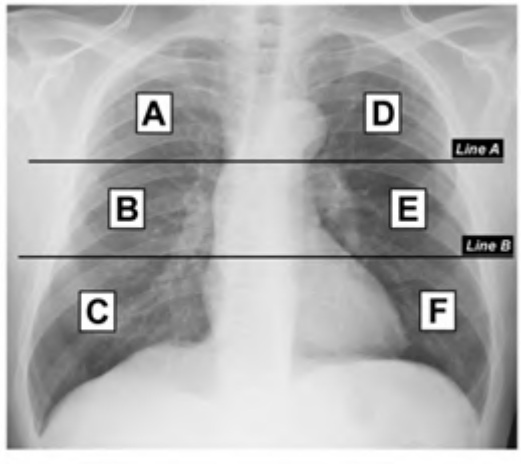

Figure 1. The 6 lung divisions on an anterior chest radiograph. A line is drawn from the inferior wall of the aortic arch. Line B is drawn from the inferior wall of the pulmonary vein. A and D are the upper zone, B and E are the middle zone, and C and F are the lower zone.[13]

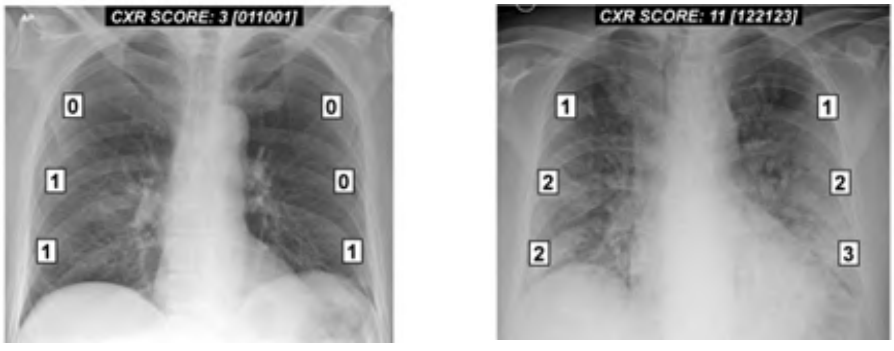

Figure 2. Example of assessing the degree of pneumonia score using the Brixia score, the top image total score: 3, the bottom image: 11

involving 592 severe-critical adult COVID-19 patients, including 240 in the tocilizumab group, the mortality rate in the tocilizumab group was 16.3% (39/240), which was lower than the control group. Both studies concluded that the combination of convalescent plasma and tocilizumab treatment was associated with improvements in inflammatory conditions and disease progression.[7,8]

METHODS

This study was conducted to evaluate the correlation between Brixia Score findings and clinical laboratory results in critically ill COVID-19 patients receiving standard therapy compared to tocilizumab at Kariadi Hospital Semarang using an analytical retrospective cohort method, with the selection of research subjects based on patient data from January 2020 to December 2021, as recorded in the medical records and the Covid Team data of Kariadi Hospital Semarang. The research subjects were patients aged ≥18 years who were hospitalized at Kariadi Hospital Semarang and had been adjusted according to the inclusion and exclusion criteria. A total of 72 individuals were gathered as research subjects, and their Brixia Score values and clinical laboratory results were examined. The evaluation of clinical laboratory results was assessed on day 3 after therapy, while the evaluation of Brixia Score values was assessed on day 9 after therapy. The study took place at the Radiology Department of Kariadi Hospital Semarang, utilizing samples consisting of laboratory results (fibrinogen, CRP, ferritin, D-dimer) and chest X-rays from hospitalized patients diagnosed with severe COVID-19 who received either standard therapy or tocilizumab. The study was conducted from March to October 2022. This study was quantitative research with a retrospective cohort design, where the dependent variables were observed, and the independent variables were obtained from patients' medical records. The target population for this research included adult patients (both male and female) aged 18 years and above, who were hospitalized with a positive diagnosis of COVID-19 and received tocilizumab or standard therapy at Kariadi Hospital Semarang. The research sample consisted of chest X-rays from patients who met the inclusion criteria (age ≥18 years, confirmed positive for COVID-19 through antigen or RT-PCR tests, hospitalized with chest X-ray findings showing opacities or pneumonia) and did not meet the exclusion criteria (no active tuberculosis lesions, no pleural effusion, lung mass, pulmonary vascular enlargement, or history of treatment with intravenous immunoglobulin or stem cell/secretome).[15]

The Brixia score values are divided into 4 groups: normal (0), mild pneumonia (1–6), moderate pneumonia (7–12), and severe pneumonia (13–18). In the tocilizumab therapy group, Brixia scores ranged from 0 to 16, while in the standard therapy group, Brixia scores ranged from 2 to 16. This study was aproved by Health Research Ethics Committee of RSUP Dr. Kariadi Semarang

RESULTS

The correlation between the Brixia score imaging and clinical laboratory results in critically ill COVID-19 patients receiving standard therapy

Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and D-dimer in convalescent plasma before therapy, with a *p-value* of 0.024 ($p < 0.05$) and a correlation coefficient of 0.377.

Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and D-dimer in convalescent plasma after therapy, with a *p-value* of 0.314 ($p < 0.05$) and a correlation coefficient of 0.359.

Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and clinical laboratory results in critically ill COVID-19 patients receiving tocilizumab therapy

Based on the correlation test using the Spearman's rank correlation coefficient, a *p-value* of less than 0.05 was not

TABLE 1
Comorbidities among patients receiving standard and tocilizumab therapies

Comorbidities	Tocilizumab group	Tocilizumab group
Hypertension	3 patients (8.3%)	3 patients (7.9%)
Type 2 diabetes mellitus	4 patients (11.1%)	7 (18.4%) patients
Benign prostatic hyperplasia	1 patient (2.8%)	–
Heart failure	2 patients (5.6%)	1 patient (2.6%)
Ischemic heart disease	–	1 patient (2.6%)
Pulmonary embolism	1 patient (2.8%)	–
Hepatitis B	1 patient (2.8%)	–
Obesity	2 patients (5.6%)	–
No comorbidity	22 patients (57.9%)	29 patients (68.5 %)

obtained, indicating that there is no significant correlation between the Brixia score and clinical laboratory results before or after tocilizumab therapy.

DISCUSSION

Hyperinflammation phase in the pathogenesis of Covid-19 infection occurs during the severe and critical phases. In the severe phase, there is a cytokine storm characterized by increased levels of CRP, D-dimer, and procalcitonin. In the critical phase, systemic inflammation occurs with elevated levels of procalcitonin, ferritin, and C-reactive protein. IL-6 and other inflammatory cytokines are also increased, leading to the failure of various organ functions. Additionally, blood coagulation disorders may occur, as indicated by elevated D-dimer and prothrombin time.[6–8]

Patients with severe-critical Covid-19 infection who were treated at Kariadi Hospital Semarang and became subjects of the study experienced an increase in Brixia Score values (Brixia Score values in this study ranged from 2 to 16). This is consistent with a previous study conducted by Zubo Wu *et al*. in 2021, which found a significant correlation between the degree of pneumonia and chest X-ray findings in critically ill Covid-19 patients. The study results showed that in patients with moderate-severe Covid-19, both in the tocilizumab therapy group and the standard therapy group, there was an increase in clinical laboratory values of inflammatory markers such as C-reactive protein, fibrinogen, ferritin, and coagulation marker D-dimer. This is in line with a study conducted by Ana Karla *et al*. in 2021, which stated that interleukin 6, ferritin, and C-reactive protein are biomarkers that increase and play an important role in the cytokine storm associated with poor prognosis in Covid-19 infections.[9,10]

Spearman rho analysis revealed a significant correlation between Brixia score and D-dimer values, both before and after therapy, in the standard therapy group. The obtained *p-value* was 0.024 ($p < 0.05$) with a correlation coefficient of 0.377 before therapy, and a *p-value* of 0.314 ($p < 0.05$) with a correlation coefficient of 0.359 after therapy. These findings are consistent with a previous study conducted by Amela Sofic, which found a significant correlation between Brixia score and D-dimer and CRP levels.[7] However, in this study, CRP levels did not show a significant correlation with Brixia score.[8] In the previous study, the inclusion criteria included patients hospitalized with a maximum CRP level of 5.0 mg/L, while in this study, the CRP levels ranged from 6–19 mg/L. In the previous study, Pairwise comparison using Shapiro-Wilk test revealed significant differences in Brixia score and D-dimer values for both tocilizumab and standard therapy ($p > 0.05$). This indicates that both therapies significantly affect the Brixia score and D-dimer values. These findings are consistent with a study conducted by Ahn *et al*. in 2021, which showed improvement in chest X-rays of Covid patients after six to ten days of convalescent plasma therapy.[4] Additionally, 12 patients demonstrated significant improvement in lung lesions on chest CT scans after five days post-transfusion of convalescent plasma. A study by Xiang Xu *et al*. also reported significant improvement in chest CT scans for severely ill Covid-19 patients treated with tocilizumab on day 14 of therapy.[4]

CONCLUSION

In this study, it is concluded that there is a significant correlation between Brixia score and D-dimer values in critically ill Covid-19 patients receiving standard therapy. This indicates a relationship between the

severity of the disease and the level of inflammation. Furthermore, both tocilizumab therapy and standard therapy showed significant differences in their effects on Brixia score and D-dimer values. These findings suggest that both therapies have distinct effects on managing inflammation and coagulation in critically ill Covid-19 patients.

For future research, it is recommended to consider the use of Brixia score in relation to more specific clinical laboratory parameters, such as interleukin-6 (IL-6), which is a key cytokine in the occurrence of cytokine storms in Covid-19 infections.[17] Additionally, further studies can broaden the scope by exploring the correlation between Brixia score and clinical severity using more diverse data in terms of age, evaluation days, and comorbidity factors. By doing so, the research outcomes will be more relevant and provide a deeper understanding of the impact of Brixia score on the clinical condition and management of severe Covid-19 patients.[19,20]

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Original Article

The Effectiveness of Macrophage Hydrolyzed VCO Cream in Healing Second Degree Burns in Wistar Rats

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Abstract

Background : Burns are a global public health issue, with many studies on topical medications that are effective in second-degree burns. Hydrolyzed VCO (hVCO) contains lauric acid, polyferol and alpha tocopherol which are beneficial in wound healing. This study was conducted to determine the effectiveness of hVCO cream macrophage formation for second degree burn wound healing in Wistar rats.
Methods : A parallel group study was conducted on thirty wistar rats randomly divided into six groups induced second degree burns. Basic cream was applied to two control groups on the 6th and 12th day, 70% hVCO was applied to two groups on the 6th and 12th day, and 100% hVCO was applied to two groups on the 6th and 12th day. Histopathological examination of macrophage formation was conducted in each treatment.
Results : The groups with hydrolyzed VCO cream on day 12 (p=0.089) had higher macrophage formation than the same hVCO group on day 6 (p=0.354). The macrophage count of hVCO in each group showed an increase.
Conclusion : 100% hVCO is effective in accelerating second degree burn wound healing in terms of macrophage count.

Keywords : Burns, hVCO, Macrophage count

INTRODUCTION

Wounds are tissue damage or loss caused by trauma from sharp or blunt objects, changes in temperature, chemical substances, electric shock explosions, or animal bites.[1] While burns are a type of trauma with high morbidity and mortality, a global public health issue, especially in low-middle income countries. World Health Organization (WHO) estimates 300,000 deaths every year worldwide due to burns, with mortality rate in 11.6 deaths per 100,000 population per year in Southeast Asia.[2,3] In Indonesia, as a tropical country with uncontrolled use of fire, it is reported that burn injuries caused about 195.000 deaths annually and ranked as 6th most unintentional injuries.[15] Health problems due to burns effect patient's physical ability to carry out daily activities, which affects psychological and socio-economic aspects.[4] Treatment for burns varies based on the depth and classification of the burn (degree 1 as epidermal burn, degree II as superficial dermal burn, degree II as mid dermal burn, and degree III as full thickness burn.[5–7] Compared with other degrees, burn wounds II (superficial and mid dermal) is most often found where there is loss of dermis layer and peripheral nerve fibers causing severe pain in patient. Treatment is expected to fasten wound healing process and restore physiological function of the skin.[6,8]

Second degree burn wound is often treated with topical medication, namely Silversulfadiazine cream. Side effects of this cream such as kidney toxicity, leukopenia, antibiotic resistance, allergic reactions, and delayed wound healing will happen if it is used for a long time.[9] Due to these adverse side effects, many studies have been carried out to find more effective and efficient active ingredients for topical medicines from natural ingredients such as Virgin Coconut Oil (VCO). VCO was made from *Cocos nucifera*. High content of phytosterols as unsaturated fatty acids makes VCO widely used in cosmetics sector as antiinflammatory agent. Topical hydrolyzed VCO is also known to have antibacterial function.[10,11] C. nucifera as the main ingredient for hydrolyzed VCO is very easy to find in tropical countries like Indonesia. The process is easy to carry out and does not require large costs. Therefore, researchers wanted to assess the effectiveness of hydrolyzed VCO cream in certain doses, especially on parameters examination of the number of macrophages in the healing phase of second degree burns in Wistar rats. This study aims to prove that hydrolyzed VCO (hVCO) can be an alternative topical medication for second degree burns with macrophages as parameter, which is known to act as a predominant and continuous source of cytokines production in burn injury.

METHODS

Research Design

This is an experimental research with randomized posttest only with parallel group design. Burn was inducted in the back of rats in 3x5cm area with stainless rod attached for 15 seconds. Basic cream was applied to two control groups on the 6th and 12th day, 70% hVCO was introduced to two groups on the 6th and 12th day, 100% hVCO was introduced to two groups on the 6th and 12th day. Histopathological examination of macrophage formation was conducted in each treatment.

Research Sample

Rattus novergicus rats aged 8–10 weeks, with body weight around 100–150 grams and male sex were selected with the inclusion criteria of rats. Mice were kept in stainless steel cages with a 12-hour light cycle. Rat food was given ad libitum.

Time and location of Research

Research and data collection were carried out for 3 months. This research was carried out in five places, namely PT. Victoria Care Indonesia for making VCO product, STIFAR Semarang Laboratory as a place for making VCO cream, LPPT FK UGM as a place for treatment of experimental animals, Anatomical Pathology section Faculty of Medicine, Sebelas Maret State University, Solo and Anatomical Pathology section Faculty of Medicine, Sultan Agung University, Semarang for histopathological examination.

Research Variable

The independent variable of this research are 70% hVCO and 100% hVCO and the dependent variable is macrophage count in pathology anatomy examination.

Research Implementation

36 male *Ratus norvegicus* rats that met the inclusion and exclusion criteria were adapted for 7 days, randomized, and inducted to second degree burn wound. Group X1 was given hVCO 70% cream for six days, group X2 was given hVCO 100% cream for six days, group X3 was given basic cream for six days, then the tissue was removed and examined. Group X4 was given hVCO 70% cream for twelve days, group X5 was given hVCO 100% cream for twelve days, group X6 was given basic cream for twelve days, then the tissue was removed and examinated.

Hydrolized VCO was made from 50 grams of oil with 70% and 100% NaOH ethanol. Cream formula was made in oil-in-water emulsion. Macrophage count was measured in immunohistochemistry examination using binocular microscope with 400x magnification and hematoxylin eosin staining.

Data Analysis

Data obtained from research observations are in the form of macrophage count. The data was tested for normality using one-way Anova test. Data analysis will be continued with Post-Hoc Test to determine differences between groups. The Kruskal Wallis Non-Parametric Test will be carried out if the data is not normally distributed. The test was then followed by Mann Whitney Test to test the mean difference between each treatment group. The *p value* of significant differences was <0.05 with 95% confidence interval. Data analysis was carried out with SPSS 25 for Windows software.

RESULTS

Descriptive Analysis

In this study, normality test was carried out by Shapiro Wilk with the results shows on Table 1.

Macrophage Count

Normality and homogeneity tests show normal data with homogeneous distribution indicated by the acquisition of a *p value* >0.05 in all groups. One Way ANOVA test showed *p value* was <0.05 indicating significant differences in all groups. The test then continued with uji Post Hoc Games Howell test to analysis each difference. However, Howell's Post Hoc Games showed that the data was not normally distributed, hence to identify further differences in macrophages count, the test continued using the Kruskal-Wallis test (Table 2).

From the results of Kruskal-Wallis difference test, it was found that there was significant differences (*p value* <0.001). To determine differences in macrophages between treatment groups, the Mann-Whitney Post Hoc test was used. The results showed significant differences in X3 group versus versus X2, X6, X4 dan X5 group; significant differences in X1 group versus versus X2, X4 dan X5 group; significant differences in X2 group versus versus X6, X4 dan X5 group; significant differences in X6 group versus versus X4 dan X5 group.

DISCUSSION

In burn injuries, macrophages play the role of phagocytosis, cleaning necrotic tissue, pathogenic microorganisms and foreign objects. These functions lead to enhancement in macrophages levels. Monocytes as leukocyte cells are recruited from the circulatory system to the site of infection or injury. Monocytes secrete proinflammatory and angiogenic factors, also differentiate into macrophages to clean extracellular debris that enters the wound within 48–96 hours after

TABLE 1
Descriptive and Shapiro-Wilk Test Results

Group	Mean ± SD	Median (Min–Max)	$p^{£}$
X3	3.73 ± 1.12	3.90 (1.80 – 4.80)	0.271*
X1	3.77 ± 3.33	3.30 (0.00 – 9.80)	0.354*
X2	11.17 ± 4.42	10.60 (6.00 – 19.40)	0.089*
X6	1.47 ± 1.24	1.80 (0.00 – 4.00)	0.296*
X4	0.07 ± 0.16	0.00 (0.00 – 0.00)	0.000*
X5	0.00	0.00	–

TABLE 2
Macrophage Kruskal-Wallis Test Results

Group	Mean ± SD	*p*
X3	3.73 ± 1.12	<0.001*
X1	3.77 ± 3.33	
X2	11.17 ± 4.42	
X6	1.47 ± 1.24	
X4	0.07 ± 0.16	
X5	0.00	

Note: * Significant ($p < 0.05$)

TABLE 3
Post Hoc Mann-Whitney Test Results

Group I	Group II	*p*
X3	X1	0.521
	X2	0.004*
	X6	0.016*
	X4	0.003*
	X5	0.002*
X1	X2	0.010*
	X6	0.146
	X6	0.013*
	X5	0.007*
X2	X6	0.004*
	X4	0.003*
	X5	0.002*
X6	X4	0.049*
	X5	0.022*
X4	X5	0.317

Note: * Significant ($p < 0.05$)

injury. Macrophages can also secrete various cytokines and chemokines to stimulate cell proliferation and collagen deposition, promoting vascularization and granulation. There are two patterns of macrophage activation, namely classical macrophage activation (M1) which acts as immune cells and inflammatory cells in the early phase of wound healing. Activation of alternative macrophages (M2) as repair cells and dominates in the later stages of wound healing.[12]

Administration of VCO was able to show changes in macrophage function, with various increasingly high doses. In this study, macrophages increase in second degree burns on days 6 and 12 tended to be higher in wound care with 70% hydrolyzed VCO cream compared to 100% hydrolyzed VCO cream and controls. This result is due to the content of single chain fatty acids in VCO which keeps the wound tissue at optimal humidity for the formation of new cells. Single chain fatty acids also play a role in preventing bacterial invasion. On the contrary, previous research which analyzed the number of neutrophils after 70% hydrolyzed VCO cream usage found that the number of neutrophils was not too high on day 6 and decreased further on day 12 compared to 100% hydrolyzed VCO cream. The increase in neutrophils in the inflammatory phase stimulates the expression of FGF and VEGF. FGF and VEGF will activate the invasion of fibroblasts produced by macrophages. Fibroblasts proliferate and produce matrix proteins such as fibronectin, hyaluronic acid, collagen and proteoglycans. Fibroblasts also form an extracellular matrix that helps keratinocyte cell migration. Overall it may be said that administration of VCO has strong anti-inflammatory properties as well as other physiologic processes.[12]

Other study showed that angiogenesis in the 70% hydrolyzed VCO cream group had the highest number of new blood vessels on day 12 compared to the 100% hydrolyzed VCO cream and control group. Angiogenesis as a part of skin components plays an important role in new tissue formed process which connected with wound healing process. Angiogenesis stimulated by vascular endothelial growth factor (VEGF), a pro-inflammatory cytokine produced by endothelial damage and also by neutrophils. Angiogenesis, collagen deposits, and granulation tissue formation are important processes that occur in this phase.[13,14]

CONCLUSION

The results of this study concluded that administration of hydrolyzed VCO cream was more effective than administration of basic cream in healing second degree burns, in terms of the function and number of macrophages in Wistar rats. The administration of hydrolyzed VCO cream was 70% and 100% more effective in healing second degree burns, on days 6 and 12 of observation, compared to administration of basic cream.

Ethical Approval
This research has received approval from the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University with Ethical Clearance.

Conflicts of Interest
The authors declare that there was no conflict of interest.

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Author of Contributions
FS, N were involved in planning and supervised the work, FS performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. FS performed the xyz calculations and statistical analysis. FS, N aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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Original Article

The Increased Superoxide Dismuatase (SOD) in Mice Infected by *Plasmodium Berghei* ANKA Treated with Nanoparticle Extract of Beetroot *(Beta Vulgaris L)*

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Abstract

Background : Malaria infection causes increased free radicals which leads to severity and decreases antioxidant activity, thus increasing the risk of severe malaria complications. Beetroot extract has active compounds that function as anti-inflammatory and antioxidants. Nanoparticles are a technology that can be used to improve drug delivery efficiency in smaller doses. The aims of this study was to prove the effectiveness of beetroot extract nanoparticles on SOD levels in mice infected with malaria and treated with artemisinin

Methods : An experimental study using a post-test-only randomized control group design. The research sample used 30 male Balb/c mice divided into 6 groups. Group 1 was the healthy group, group 2 was the infected group without treatment, group 3 was the infected group with artemisinin treatment, group 4 was the infected group with artemisinin treatment and 50 mg/kgBW/day beetroot extract nanoparticles, group 5 was the infected group with artemisinin treatment and 100 mg/kg BW/day beetroot extract nanoparticles, and group 6 was the infected group with artemisinin treatment and 200 mg/kg BW/day beetroot extract nanoparticles. Beetroot extract and artemisinin supplementation were given after parasitemia index > 1% and given for 4 days. On the 5th day after therapy, serum SOD levels were measured using ELISA.

Results : The measurement of SOD levels in the artemisinin group supplemented with nanoparticle extracts of beetroot at doses 100–200 mg/KgBW were 21,48–21,59 ng/ml. Kruskal Wallis and Mann Whitney test showed that they are significantly higher serum SOD levels compared to the infected mice group (p<0.05).

Conclusion : Supplementation of beetroot extract nanoparticles has an antioxidant effect by increasing SOD levels in mice infected with malaria and receiving artemisinin therapy.

Keywords : malaria; antioxidant; betacyanin, artemisinin

INTRODUCTION

Malaria is a parasitic infectious disease that is a global health priority, with 241 million cases reported worldwide in 2020 in 85 endemic countries. Indonesia is one of the countries with a high incidence of malaria, reaching 254,055 cases in 2020. This has become a concern for the government to gradually implement a malaria elimination program.[1] The formation of free radicals in malaria infection can be caused by two factors, those are the immune response to malaria and produced by malaria itself. Activation of the immune system will increase the production of reactive oxygen species (ROS) during phagocytosis as an effort to eliminate plasmodium. Additionally, during the erythrocytic phase, plasmodium will degrade hemoglobin and release free heme and H_2O_2, which are oxidative to host tissues. Excessive ROS production in malaria infection causes redox imbalance, which triggers the body to combat free radicals using antioxidants. However, there is a lack of antioxidant activity for host defense during infection.[2,3]

Superoxide dismutase (SOD) plays a role in converting free radicals into hydrogen peroxide, which will subsequently be degraded by catalase and glutathione. Several studies have shown a relationship between SOD activity and tissue damage, which SOD level can serve as a marker of malaria severity.[4] This creates an opportunity for the development of antioxidant supplementation in malaria infection.

Beetroot is a plant from the Amaranthaceae family that contains bioactive compounds such as polyphenols, carotenoids, flavonoids, betanin, and betalains. Several studies have shown that beetroot extract has antioxidant and anti-inflammatory effects.[5,6] Beetroot extract has a stronger antioxidant effect than vitamin C due to the presence of betasianin. Beetroot extract supplementation also protects against free radicals in rats induced by a high-fat and fructose diet by increasing the expression of SOD2 and CAT genes.[7] The active compounds in natural materials cannot penetrate cells effectively, which reduces their effectiveness. It can be solved by increasing their effectiveness and absorption, one of which is through the application of nanomedicine technology. Nanoparticles are a technology that can be used to improve drug delivery efficiency in smaller doses by increasing the drug's absorption rate and reducing enzyme biodegradation.[8–10]

Several studies have shown that beetroot extract supplementation at a dose of 100–300 mg/kgBW/day provides anti-inflammatory and antioxidant effects. However, there is no current research on beetroot extract nanoparticles.[11,12] Therefore, this study uses a dose of 50, 100, and 200 mg/kgBW/day for 4 days of beetroot extract nanoparticles. The nanoparticle extracts of beetroot in this study were prepared using the ionic gelation method using chitosan and NaTPP.

This study aims to determine the effect of beetroot extract nanoparticle supplementation on SOD levels in mice infected with malaria and treated with artemisinin.

MATERIALS AND METHODS

An experimental study was done with a post-test-only randomized controlled group design. The study was conducted at the Pharmacology and Parasitology Laboratory, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada Yogyakarta, Indonesia, after obtaining ethical approval from the Health Ethics Committee. The Ethical clearance issued by The Health Research Ethics Committee Faculty of Medicine Universitas Diponegoro.

Animals and Experimental Groups

The study used 30 male Balb/c mice aged 6–8 weeks with a body weight of 25–35 grams, divided into 6 groups. The research group division was as follows:

Baseline group: Healthy mice

Negative control group: Mice inoculated with *Plasmodium berghei* ANKA

Positive control group: Mice inoculated with *Plasmodium berghei* ANKA and treated with artemisinin (ART) at a dose of 0.036 mg/gr BW

Treatment group I: Mice inoculated with *Plasmodium berghei* ANKA and treated with artemisinin (ART) at a dose of 0.036 mg/gr BW + 50 mg/kg BW beetroot extract nanoparticles

Treatment group II: Mice inoculated with *Plasmodium berghei* ANKA and treated with artemisinin (ART) at a dose of 0.036 mg/gr BW + 100 mg/kg BW beetroot extract nanoparticles

Treatment group III: Mice inoculated with *Plasmodium berghei* ANKA and treated with artemisinin (ART) at a dose of 0.036 mg/gr BW + 200 mg/kg BW beetroot extract nanoparticles.

The experimental animals in this study were a malaria model with inoculation using *Plasmodium berghei* ANKA. The *Plasmodium berghei* ANKA isolate was obtained from parent mice with a parasitemia level of 20% and was injected intraperitoneally into infected mice at a volume of 0.2 ml containing 10^7 parasitized erythrocytes. Parasitemia was calculated on day 3 post-inoculation, and after parasitemia reached >1%, artemisinin and nanoparticle extracts of beetroot were administered for 4 days.

Preparation of Extraction and Nanoparticles

The material used in this study was beetroot extract nanoparticles. The beetroot extract was made using the maceration method using 96% ethanol, then filtered and evaporated using a rotary evaporator until a concentrated beetroot extract was obtained. Nanoparticles were made using a formulation of beetroot

extract, chitosan, and Na TPP (ionic gelation method). Chitosan and NaTPP were used in a ratio of 4:1, and the weight of the beetroot extract was adjusted to make doses of 50 mg, 100 mg, and 200 mg. The resulting beetroot extract nanoparticles were then characterized using a Particle Size Analyzer (PSA) to measure particle size and polydispersity index.

Blood Sample Collection and Biochemical Analysis

Specimen collection and termination were performed on day 5 post-therapy, followed by an examination of SOD levels using an ELISA Kit from Bioassay Technology Laboratory (BT Lab) Cat No. E2608Mo. Blood samples were taken through the eye vein using a microhematocrit. Blood serum was separated by centrifugation after 15 minutes. All animals were anesthetized with 0,5 ml ketamin then cervical dislocation was performed.

The measurement of SOD level using a microplate then add 50 standard to standard well. Add 40 µl sample to sample wells and then add 10 µl Mouse SOD1 antibody to sample wells, then add 50 µl streptavidin-HRP to sample wells and standard wells. Mix well then cover the plate with a sealer. Incubate 60 minutes at 37°C. Remove the sealer and wash the plate 5 times with wash buffer. Add 50ul substrate solution A to each well and then add 50 µl substrate solution B to each well. Incubate plate covered with a new sealer for 10 minutes at 37°C in the dark. Add 50 µl Stop Solution to each well, the blue color will change into yellow immediately. Determine the optical density (OD value) of each well immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.

Statistical Analysis

The results of SOD level were then analyzed to determine the significant difference in the supplementation of beetroot extract nanoparticles on SOD levels. The results of the homogeneity test using the Shapiro-Wilk test showed that the data was not normally distributed even after data transformation, so the difference test was analyzed using the Kruskall-Wallis test followed by the Mann-Whitney test to determine the differences between groups in this study. The results of statistical analysis were presented using median (minimum-maximum) and *p-value*, in which a *p-value* <0.05 is considered significantly different.

RESULTS

Characterization of Beetroot Extract Nanoparticles

The characterization of beetroot extract nanoparticles showed that a dose of 50 mg/kgBW had a dark brown color, while at a dose of 100 mg/kgBW was yellowish brown, and at a dose of 200 mg/kg BW was yellow. No sediment in all formulations was found. The characterization of beetroot extract nanoparticles at various doses describes particle size and molecular dispersion index as shown in Table 1 and Figure 1.

TABLE 1
Formulation and Particle Size Analysis

Symptoms AR	Extract Weight	Chitosan Weight	NaTPP Weight	Z Average	Pd Index
Nanoparticle Extract of Beetroot 50 mg/kbBW	150 mg	80 mg	20 mg	282.1 nm	0.381
Nanoparticle Extract of Beetroot 100 mg/kbBW	300 mg	80 mg	20 mg	327.3 nm	0.281
Nanoparticle Extract of Beetroot 200 mg/kbBW	600 mg	80 mg	20 mg	543.7 nm	0.769

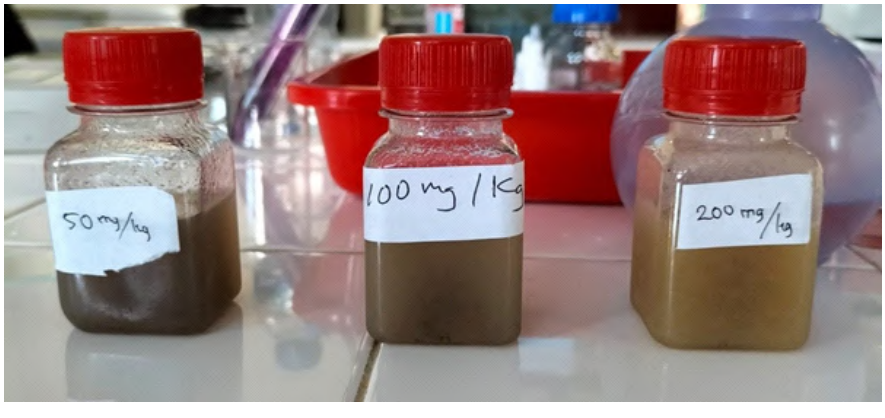

Figure 1. Nanoparticle Extract of Beetroot at doses 50 mg/kgBW(a), 100 mg/kgBW (b) dan 200 mg/kgBW (c)

TABLE 2
Statistical Analysis of SOD Levels in Beetroot Extract Nanoparticle Supplementation

Group	Median (Min–Max) ng/ml	Kruskal-Wallis Test
Baseline	23.89 (21.91 – 41.17)	p = 0.010*)
Negative control	14.44 (13.26 – 19.29)*	
Artemisinin	22.92 (17.32 – 26.22)#	
ART+NEB 50 mg/kgBW	14.67 (13.29 – 21.94)*	
ART+NEB 100 mg/kgBW	21.59 (18.21 – 26.54)#	
ART+NEB 200 mg/kgBW	21.48 (18.89 – 22.77)*#	

Data as presented as median (n=5 for each group)
* p<0.05 compared to baseline;
# p<0.05 compared to negative control

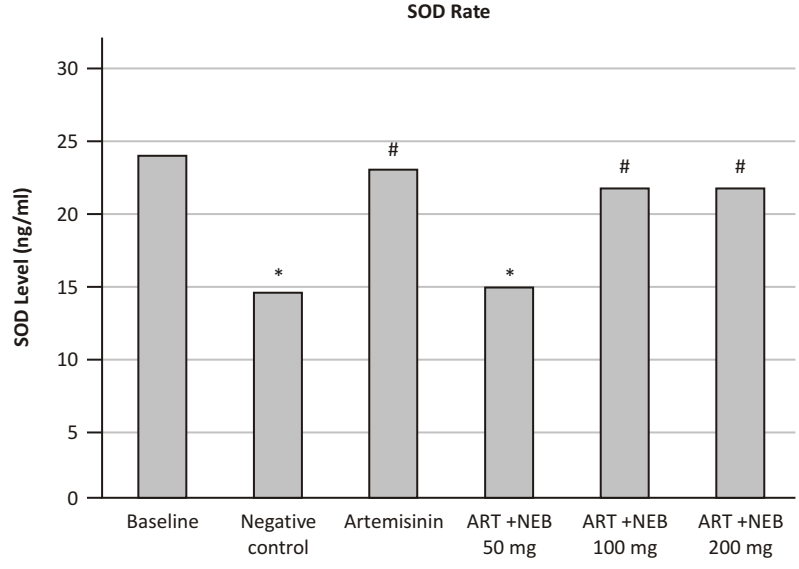

Figure 2. Effect of nanoparticle extract of beetroot in SOD level on mice inoculated with *Plasmodium berghei* ANKA and treated with artemisinin. * p<0.05 compared to baseline; # p<0.05 compared to negative control.

Superoxide Dismutase (SOD) serum Level

Examination of SOD Levels using Serum Specimens with ELISA Method. The examination was read using an ELISA reader at a wavelength of 456 nm and the following results were shown in Table 2 and Figure 2.

The result showed that the SOD level in normal mice is 23.89 ng/ml. Malaria infection affects SOD levels in mice, where the negative control group had the lowest SOD level of all groups, at 14.44 ng/ml. Artemisinin administration in the positive control group showed a higher SOD level than the negative control group, at 22.92 ng/ml. Supplementation with beetroot extract nanoparticles in the treatment groups showed varying results in increasing SOD levels, namely 14.67 ng/ml at a dose of 50 mg/kg BW/day; 21.59 ng/ml at a dose of 100 mg/kg BW/day; and 21.48 ng/ml at a dose of 200 mg/kg BW/day.

Kruskal-Wallis test showed a significant difference between the treatment groups, and the Mann-Whitney test was used to determine which groups were significantly different. Mann Whitney test showed a significant difference in SOD level between the negative control group and the combination group of artemisinin and NEB at 50 mg/kg BW compared to the baseline group, which is the SOD level in these groups was significantly lower than the baseline group. Meanwhile, the negative control group showed a significant difference with the artemisinin group and combination with NEB 100–200 mg/kg BW, in which the SOD level in the combination of artemisinin and NEB were significantly higher. However, there was no difference in SOD level between artemisinin groups and supplementation with NEB.

DISCUSSION

Supplementation with beetroot extract nanoparticles could be a promising future complementary therapy along with artemisinin therapy for malaria infection. Malaria infection by *plasmodium* can lead to oxidative stress and an imbalance in antioxidant activity in the body.[13] This study showed that the lowest SOD levels were found in the group of mice infected with malaria without treatment, which proves that malaria infection causes an increase in the production of free radicals that trigger oxidative stress and inhibit antioxidant activity. Malaria infection triggers the immune system to eliminate parasites, thereby increasing pro-inflammatory cytokines. This causes an increase in the production of free radicals that can harm the body by damaging cells and tissues and causing an imbalance in antioxidant activity in the body. SOD plays an important role in controlling free radicals that can lead to serious complications in malaria patients. SOD acts as an antioxidant by converting free radicals into hydrogen peroxide (H_2O_2), which is then removed by catalase and glutathione. This highlights the importance of supplementation with antioxidant therapy as an adjunct to antimalarial drugs to control malaria infection and prevent the occurrence of serious complications of malaria later on.[4,14,15]

Supplementation with beetroot extract nanoparticles in mice infected with and receiving artemisinin treatment showed higher SOD levels. Beetroot contains active compounds such as betalains, nitrates, and phenolic compounds. Betalains are the main content of beetroot which will be converted into betacyanins and betaxanthins, while betacyanins will be converted into betanin which has antioxidant and anti-inflammatory properties. Betanin has antioxidant properties because it can scavenge radicals, donate hydrogen and electrons, decompose peroxides, or quench singlet oxygen. Betanin has a hydroxyl group from the phenol group that is similar to the phenolic antioxidant ethoxyquin, which gives betanin its properties as a hydrogen donor and free radical reducer.[5,16,17]

Betanin also plays a role in regulating the activity of antioxidant enzymes by modifying cysteine residues and breaking the Kelch-like repressor protein ECH-associated Protein 1 (KEAP1) and Nuclear factor erythroid 2 related factor 2 (Nrf2) bonds so that Nrf2 accumulates and can bind to Antioxidant response element (ARE). This binding will upregulate genes encoding antioxidants and phase II enzymes. In addition, betanin also activates mitogen-activated protein kinase (MAPK) which can lead to phosphorylation and stabilization of Nrf2, thereby increasing the translocation of Nrf2 in the nucleus. Upregulation of Nrf2 target genes will stimulate the activity of antioxidant enzymes and restore the redox balance in the body. This leads to the role of SOD as an antioxidant to convert free radicals into H_2O_2 and converted into H_2O and O_2 by catalase so that cells and tissues are protected from the effects of oxidative stress and prevent the occurrence of serious complications in malaria.[18–21]

The antioxidant activity of beetroot is related to its betalain content. This is also due to nitrates, amino acids, peroxidase enzymes, and β-glucosidase, which act as radical scavengers. The results of this study are consistent with research showing that beetroot juice has potential anti-plasmodial effects by reducing the parasitemia index and potentially serving as an adjuvant therapy for artemisinin. The free radical effects produced during inflammation and artemisinin administration can be balanced with the antioxidant effects of beetroot extract nanoparticles, thereby reducing tissue damage and preventing severe malaria.[22–24]

CONCLUSION

Supplementation with beetroot extract nanoparticles in malaria-infected mice with artemisinin treatment showed antioxidant capacity that can control free radicals by increasing SOD activity. Therefore, supplementation with beetroot extract nanoparticles can be used as an adjuvant therapy for malaria treatment to prevent the occurrence of severe malaria complications.

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Original Article

Factors Associated with Survival Rate in Biliary Atresia Patients Following Kasai Surgery

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Abstract

Background : Biliary atresia is the most frequent cause of obstructive jaundice leading to liver fibrosis, end-stage liver disease, and death. Kasai surgery offers a bridge to attenuate liver fibrosis progression through reconstruction of the biliary system. The success of the Kasai procedure depends on the presence of jaundice, age at the time of surgery, clay-colored stool, and bilirubin counts. This study aimed to investigate and predict the death incidence of Biliary atresia patients following Kasai Surgery in our institution.
Methods : We conducted a case-control study from March 2020 to January 2022 at Kariadi General Hospital, Semarang, Indonesia. We collected data related to gender, age at surgery, albumin level pre and post-surgery, total and direct bilirubin before and after surgery, and the presence of ascites. Bivariate analysis using the Chi-Square test with OR (95% CI) was performed to analyze the risk factors in BA patients following the Kasai procedure.
Results : 19 patients with biliary atresia underwent the Kasai procedure with a survival rate of 68.4%. Bilirubin levels ≥10 mg/dL before (p=0.033, OR 11.25) and after (p=0.025, OR 11.00) the Kasai procedure, and the presence of ascites (p=0.005) were significant factors associated with mortality cases. However, a combined multivariate analysis of these factors did not show any significant relationship with outcomes.
Conclusion : Bilirubin exceeding 10 mg/dL before and after the Kasai procedure and the presence of Ascites was a marker for poor outcomes for biliary atresia patients following the Kasai procedure.

Keywords : Biliary atresia, Kasai procedure, ascites

INTRODUCTION

Biliary atresia (BA) is the most commonly identified cause of obstructive jaundice in the first three months of life. Biliary atresia (BA) is a potentially fatal disease in infants, where there is progressive obliterative cholangitis that affects the intra and extrahepatic tracts as persistent cholestasis. This often results in liver fibrosis, end-stage liver disease, and death.[1,2] The incidence rate of biliary atresia is 1:19000 compared to live births in Canada.[3] The incidence rate in North America and Europe ranges from 1:8000–1:16000, while in Asia it ranges from 1:5000–1:8000.[4,5] In Yogyakarta, Indonesia, the prevalence of BA is reported to be 1:7000.[6] BA should be treated immediately in the early stages of life to avoid biliary cirrhosis and liver failure. The main surgical procedure used to treat BA is Kasai surgery. However, only 65% of BA patients remain alive after Kasai's surgery within 5 years.[7] Only less than 30% of patients were able to survive long-term with their liver after Kasai, and most eventually died or received a liver transplant.[8] Although liver transplants are constrained by a lack of donors, high costs, and the use of lifelong anti-rejection drugs after surgery, liver transplants from living donors to treat biliary atresia have made rapid progress in recent years. Various methods are used to identify the prognostic factors of Kasai surgery outcomes, such as age, bilirubin profile after surgery, aspartate aminotransferase (AST) after recovery from Kasai surgery, recurrent cholangitis, etc. However, the results still show some conflicting findings,[9] so the prognosis of AB patients undergoing Kasai surgery is uncertain. Therefore, the researcher investigated the relationship between prognostic factors and the mortality rate of BA patients after Kasai surgery in the Indonesian population, especially in Kariadi Semarang Hospital.

MATERIALS AND METHODS

Patient samples

A retrospective study using the medical records of babies with BA who underwent Kasai surgery was conducted at Kariadi Hospital, Semarang, Indonesia. Researchers analyzed 19 BA patients, with 13 male patients and 6 female patients, from March 2020 to January 2022.

Prognostic factors

The researchers evaluated and correlated the following prognostic factors and the survival rate of BA patients after Kasai surgery: sex, age at Kasai surgery, and total bilirubin and albumin levels before and after the Kasai procedure. Researchers determined patients who survived with a survival rate of 1 year.

The researchers divided the total serum bilirubin (TB) levels from the samples before and after Kasai surgery into high (<10 mg/dL) and very high (≥10 mg/dL). The researchers divided serum albumin levels from samples before and after Kasai surgery into normal (≥3.5 g/dL) and abnormal (<3.5 g/dL). Total serum bilirubin and albumin levels were measured in the first week before and after Kasai surgery. Ascites are categorized as present when they are clinically detected or found by sonography or intraoperative methods in quantities greater than *traces* or s*cants*.

Statistical analysis

The data is presented as a frequency. Univariate analysis was carried out to obtain the frequency of each variable. Bivariate analysis using *the Chi-Square* test was carried out to determine the relationship between prognostic factors and the survival rate of BA patients. Multivariate analysis aims to find out which prognostic factors are more influential. This study was aproved by Health Research Ethics Committee of RSUP Dr. Kariadi Semarang.

RESULTS

Nineteen BA patients were identified from March 2020 to January 2022. Researchers identified the survival rate after the Kasai operation to be 68.4%. Table 1 presents basic clinical and biochemical data for BA patients.

First, the researchers analyzed the relationship between the characteristics of BA patients and their survival rates. Bilirubin greater than 10 mg/dL before (p=0.05, OR 11.25) and after (p=0.046, OR 11.00) Kasai procedure and the presence of Ascites (p=0.021) were significant factors in mortality cases. (Table 1).

Multivariate analysis using tests cox-regression in the three variables above, the mortality of the Kasai procedure in BA patients showed the following results (Table 2).

The results of *the cox-regression* test on the output of total bilirubin before surgery, total bilirubin after surgery, and ascites were found to be insignificant (p>0.05 value) to the mortality of the Kasai procedure.

DISCUSSION

The Kasai procedure aims to cut off the blocked extrahepatic bile ducts and restore bile flow.[11] If this procedure fails to eliminate jaundice and/or complications associated with biliary cirrhosis, a secondary liver transplant (LT) is required.[12] Overall, 20% of patients can reach the age of 20 with their original heart, and 10% can reach the age of 30.[13,14] In developed countries, biliary atresia patients are generally referred to undergo Kasai surgery before the age of sixty days.

Albumin levels at one month and three months after surgery were able to predict the survival rate of BA patients after Kasai surgery at Sardjito Hospital Yogyakarta, Indonesia.[15] Patients with albumin levels of

TABLE 1
Shows the basic clinical and biochemical data of BA patients

Variable		Outcome		*p*	OR (95% CI)
		Died (*n*=6) *n* (%)	Control (*n*=13) *n* (%)		
Gender	Man	4 (66.7)	9 (69.2)	0.911$^{\alpha}$	0.89 (0.11 – 7.02)
	Woman	2 (33.3)	4 (30.8)		
Age at the time of surgery	< 60 days	1 (16.7)	4 (30.8)	0.516$^{\alpha}$	0.45 (0.39 – 5.21)
	≥ 60 days	5 (83.3)	9 (69.2)		
Albumin before surgery	< 3.5 g/dL	1 (16.7)	2 (15.4)	0.938$^{\alpha}$	0.90 (0.06 – 12.58)
	≥ 3.5 g/dL	5 (83.3)	9 (69.2)		
Albumin after surgery	< 3.5 g/dL	3 (50.0)	7 (53.8)	0.876$^{\alpha}$	0.86 (0.12 – 5.94)
	≥ 3.5 g/dL	3 (50.0)	6 (46.2)		
Total bilirubin before surgery	≥ 10 mg/dL	5 (83.3)	4 (30.8)	0.033$^{\alpha*}$	11.25 (0.97 – 130.22)
	< 10 mg/dL	1 (16.7)	9 (69.2)		
Total bilirubin after surgery	≥ 10 mg/dL	4 (66.7)	2 (15.4)	0.025$^{\alpha*}$	11.00 (1.14 – 106.43)
	< 10 mg/dL	2 (33.3)	11 (84.6)		
Ascites	Yes	3 (50.0)	0 (0)	0.005$^{\alpha*}$	–
	Not	3 (50.0)	13 (100)		

Description: *Significant bivariate test (p<0.05); $^{\alpha}$ Chi-Square test

TABLE 2
Multivariate Test Results

Variable	*p*	OR	95% CI
Bilirubin total pre op	0.946	0.000	0.000 – 7.710
Bilirubin total post op	0.662	0.537	0.033 – 8.727
Ascites	0.230	0.190	0.013 – 2.865

Description: * Significant (p < 0.05)

<3.5 g/dL at one month and three months after surgery had worse prognosis (~4 and ~28-fold, respectively) compared to those with albumin levels of ≥3.5 g/dL.[16] Low albumin causes ascites and increases the mortality rate of infants with chronic liver disease. Higher preoperative mean serum albumin levels and postoperative jaundice are associated with long-term survival for original liver transplant patients.[17] Unfortunately, the researchers' statistical analysis stated that there was no significant association between albumin measured at 1 week before and after surgery on the survival rate of BA patients. Serum albumin and total bilirubin in the first month after Kasai surgery were not significant prognostic factors in determining the survival of BA patients at Sardjito Hospital.[15] Total bilirubin >2mg/dL and albumin <3.5g/dL at 3 months post-operative to Kasai are also significant predictors of future transplant needs.[18]

Although 60% of babies with BA will initially experience a recovery in bile flow after surgery, liver fibrosis is progressive, and portal hypertension (PHT) occurs in most children. Manifestations of PHT, including splenomegaly with hypersplenism, esophageal and gastrointestinal varicose veins, and ascites, are associated with significant morbidity and mortality. Ascites occur in about one-third of patients with PHT. Diuretic therapy and reduction of excess sodium intake are the main treatments in children. Ascites associated with low serum albumin levels may obtain good results from intravenous 20% or 25% albumin infusion followed by IV furosemide.

In diuretic refractory ascites associated with respiratory disorders, difficulty eating, or urine retention, recurrent large-volume paracentesis may be necessary. Researchers identified that ascites after surgery can predict the survival rate of BA patients after Kasai surgery. Ascites are a sign of liver cirrhosis. Patients with ascites after surgery have a worse prognosis compared to patients without ascites Ascites and sepsis are strong prognosis factors against poor post-operative prognosis in Kasai.[17–19]

Although some conflicting results have been published regarding the impact of age during surgery, a series of large studies simultaneously show that the short-term outcomes of Kasai's surgery will be better when the surgery is performed early in life. Most of the research patients underwent Kasai surgery at more than 60 days of age. It has been proven that earlier surgical age has a good prognosis for the survival of BA patients.[20,21] but this hypothesis is not always confirmed.[14,22,23] An effective BA screening program is important because early diagnosis can allow for an earlier age for Kasai portoenterostomy, significantly improving short- and medium-term outcomes, including *jaundice clearance rates* (JCR), *native liver survival rates* (NLSR), and overall mortality.[24–27] A retrospective study in 2015 also found that liver transplant rates were significantly lower in BA patients who underwent Kasai surgery at 60 days of age than those who underwent surgery at more than 60 days of age.[28] Researchers believe the need for LT could be reduced if the average age at Kasai surgery was reduced to age 50 or even 45 days. However, the best time for Kasai surgery to get better outcomes for BA patients is still controversial.[10,16] Some studies have shown that age is not a determining factor in the success of the Kasai operation.[14,29]

This study was able to predict the survival rate of biliary atresia patients after Kasai surgery based on data from 1 week after surgery. Although the sample was relatively small, this study could provide insight into postoperative management after Kasai surgery.

CONCLUSION

Bilirubin levels exceeding 10 mg/dL before and after the Kasai procedure and the presence of Ascites are markers of poor outcomes in biliary atresia patients after the Kasai procedure.

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Original Article

Correlation between the Severity of Chronic Rhinosinusitis and The Degree of Osteitis Based on Computerized Tomography Evaluation

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Abstract

Background : The incidence of chronic rhinosinusitis (CRS) is increasing every year, characterized by inflammation of the nasal and paranasal sinuses mucoperiosteum for more than 12 weeks. The inflammatory process of CRS sometimes spreads to the surrounding bone tissue resulting in osteitis. Computerized tomography scan (CT scan) can assess the degree of mucosal inflammation using the Lund-Mackay score (LMS) while the degree of bone thickening and remodelling are assessed with Global osteitis score (GOS) and Kennedy osteitis score (KOS). This study was aimed to evaluate the correlation between CRS severity assessment using LMS and osteitis severity assessment using GOS and KOS

Methods : A retrospective analysis using a cross-sectional design was conducted that included 63 CT scans of the paranasal sinus of CRS patients. The spearman rank test was used to analyze data.

Results : Assessment using LMS showed 44% patients were classified as severe, while 29% and 27% patients were classified as moderate and mild respectively. Global osteitis score showed 2% patients were categorized as severe, while 22% and 46% patients were categorized as moderate and mild respectively, and 30% patients were not significant. Based on KOS assessment, it was found that 3% patients were classified as severe, while 38% and 59% patients were classified as moderate mild respectively. There was a significant correlation between CRS severity using LMS and GOS (p 0.000) with rho= 0.951. There was a significant correlation between CRS severity using LMS and KOS (p 0.000) with rho value= 0.452.

Conclusion : This study shows a significant correlation between CRS severity assessment using LMS and bone thickening and remodelling assessment using GOS and KOS. In comparison with KOS, GOS has stronger relationship with LMS.

Keywords : chronic rhinosinusitis; Lund-Mackay CT Score; Global Osteitis Score; Kennedy Osteitis Score

INTRODUCTION

Chronic rhinosinusitis (CRS) is inflammatory of the nasal periosteum lining and paranasal sinuses that last more than 12 weeks or more than 3 recurrence episodes in the 6 months period.[1] The CRS related-paranasal sinuses mucosal changes can be driven by two etiologies; allergy and non-allergic factors. Allergic mediated-CRS is characterized by predominance of eosinophil in the nasal mucous and secretions, while non-allergic CRS is characterized by the presence of purulent secretions and predominance of neutrophil in the mucous layer. Clinical symptoms of CRS includes nasal congestion, colored nasal discharge, facial pain and smell disorder or cough.[2]

The incidence of chronic rhinosinusitis in the United States is 14.1% among adult population. Indonesian Ministry of Health in 2013 stated that rhinosinusitis was the 25th most prevalent disease accounting for 102.817 patients in the hospital. Between January and August 2016, Rhinology division of Otorhinolaryngology department of dr. Cipto Mangunkusumo General Hospital reported 435 rhinology patients in which 69% of them was diagnosed rhinosinusitis indicated for functional endoscopic sinus surgery (FESS).[3]

The inflammatory process of CRS is not limited to the mucosa, but sometimes spreads to the surrounding bone tissue and involves the sinus bone below the mucosa, resulting in osteitis.[4,5] Bone involvement in CRS are referred as osteitis/osteomyelitis/hyperostosis/bone hyperplasia and neo-osteogenesis. The term of osteitis is recommended due to the absence of marrow in the flat bones around the sinuses except in the frontal sinus.[6]

The gold standard of radiology examination for CRS diagnosis is Computerized Tomography scan (CT scan) of paranasal sinuses without contrast; using Lund Mackay Score (LMS) method for interpreting the degree of sinusitis.[7,8] The Lund Mackay scoring system has limitations due to nonlinearity and limited sensitivity for mild to moderate disease assessment.[9] Osteitis is defined as hyperostosis, bone involvement, new bone formation, neo-osteogenesis or osteoneogenesis, and chronic osteomyelitis in any sinus wall. Severity of osteitis in CRS can be assessed using Global Osteitis Score (GOS) and Kennedy Osteitis Score (KOS).[2,4]

The CRS assessment using LMS cannot determine recurrences and prognosis of CRS.[9] Many clinicians considered osteitis grading is better than LMS. To date, there is no study comparing osteitis severity score between GOS and KOS. Therefore, we want to examine the correlation between the severity of CRS using LMS method and osteitis grading using GOS and KOS.

METHODS

We conducted a retrospective study with cross-sectional design. Data were gathered from electronic medical records of patients aged 18 years or older with positive result of plain paranasal sinuses CT between June 2022 and May 2023 in Radiology Unit of Dr. Kariadi General Hospital, Semarang. Patients with sinonasal tumours, maxillofacial injury, and history of nasal or sinus surgery were excluded. This study was approved by Health research ethics committee of RSUP Dr. Kariadi Semarang.

The sinusitis severity was assessed using the Lund Mackay Score with a total score of 24. The mucosal thickening in each right and left sinus was categorized into 0 (no abnormality), 1 (partial opacity), and 2 (total opacity), while the right and left osteomeatal complex were classified into 0 (no occlusion) and 2 (closed osteomeatal complex).[7,8,10] The classification of osteitis severity was based on the Global Osteitis Score assessed in 10 sinuses (right and left side of frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid sinuses), and categorised as no osteitis (score <5), mild (score 5–20), moderate (score 20–35), and severe (score >35). The Kennedy Osteitis Score were classified into 0 (<3mm), 1 (3–5 mm), and 2 (> 5mm).[11,12]

The CT scan examination was conducted using a Siemens Syngovia Sensation 128 slice CT and General Electric Optima 16 slice CT. The CT without contrast of paranasal sinuses of axial and coronal planes with field of view paranasal sinuses 150–200 mm, window width 2000, window centre 200; scanner setting: kVp: 120 mAs; 200, and pitch: 1.4.

Statistical software of SPSS 20.0 was used. The Spearman rank test was used to analyse data as the quantitative variables were not normally distributed. All conclusions were based on significance level of $p<0.05$ and are confirmed by correlation coefficient.

RESULTS

Sixty-three patients who met the inclusion and exclusion criteria were assessed; consisting of 26 (41.3%) female and 37 (58.7%) male subjects. The majority of subjects were in the age group of 18–77 years with the average age was between 18–30 years followed by 18 patients (27%) aged 18-30 years, 9 patients (14%) aged 31–40 years, and 13 patients (20%) aged 41–50 years, 14 patients (21%) aged 51–60 years, and 9 patients (14%) aged older than 60 years old.

The lowest and highest value of the Lund-Mackay CT score were 1 and 24 respectively with mean score and standard deviation of 10 and 7 respectively. The lowest and highest value of the Global Osteitis Score were 1 and 38 respectively with the mean score and standard deviation of 13 and 11 respectively. The lowest and highest value of the Kennedy Osteitis Score were 0 and 8 respectively with mean score and standard deviation of 1 and 2 respectively. The most common severity in osteitis was mild either with Global Osteitis Score (46%) or

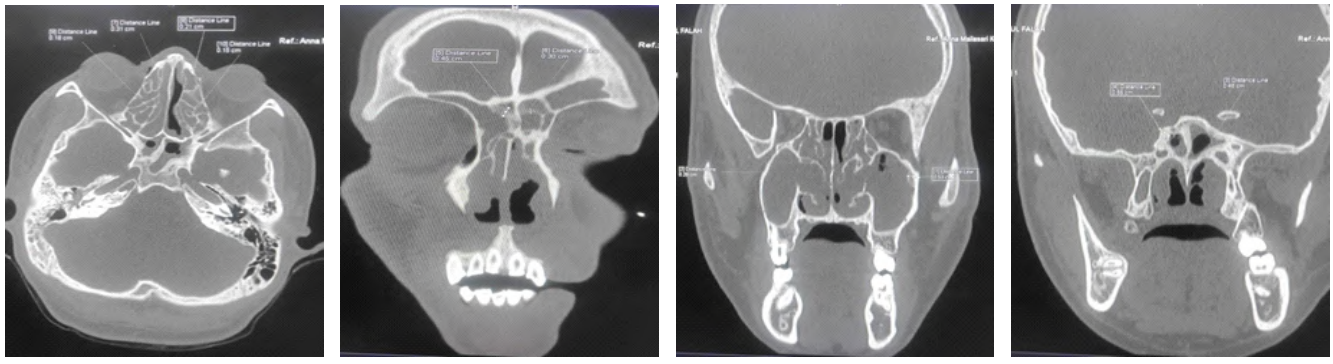

Figure 1. Measurement of the rhinosinusitis severity, Lund Mackay CT score (LMS) = 22, Global Osteitis Score (GOS) = 38 and Kennedy Osteitis score = 8

TABLE 1
Characteristic of Paranasal Sinuses Severity Score

Characteristis		Percentage
Lund-Mackay CT Score	Mild	17 (27%).
	Moderate	18 (29%)
	Severe	28 (44%)
Global Osteitis Score	Mild	29 (46%)
	Moderate	14 (22%)
	Severe	1 (2%)
Kennedy Osteitis Score	Mild	37 (59%)
	Moderate	24 (38%)
	Severe	2 (3%)

Kennedy Osteitis Score (59%).

We found a significant positive correlation between Lund-Mackay Score and Global Osteitis Score (p=0.000 and r= 0.951) with strong correlation coefficient of >0.70 (Figure 2). There was a significant positive correlation between Lund Mackay Score and Kennedy Osteitis Score (p=0.000 and r=0.452 with moderate correlation coefficient of 0.40- 0.70 (Figure 3).

DISCUSSION

The study determined CRS with and without nasal polyps shows the age-specific prevalence estimates varied between 18.8 (95% CI, 18.7–18.9) and 23.3 (95% CI, 23.1–23.5) per 1000 CI, 23.1–23.5) per 1000 population during 2004–2005 to 2013–2014, and no clear increasing trend was found. Based on age group, the prevalence of CRS with nasal polyps increases with age in adults (≥18 years) and is particularly pronounced after the age of 40 years, whereas CRS without nasal polyps is more prevalent at the age less than 40 years.[1] This is in accordance with the results obtained in this study with most rhinosinusitis patients in young adult and incidence rate decreased among patients older than 60 years.

Osteitis is a process of simultaneous increased activity of osteoblasts and osteoclasts in varying proportions resulting in disruption of flat bone formation and immature woven bone formation.[6] Osteitis is also defined as a process of new bone formation and bone remodelling within the paranasal sinuses, and is characterized by thickening of the periosteum, new woven bone formation, bone resorption, and fibrosis.[13] The presence of chronic inflammation in RSK that is not limited to the mucosa can cause inflammation to the surrounding bone tissue and especially involve the sinus bone under the mucosa resulting in osteitis.[4,5] The severity of bone thickening of the paranasal sinuses assessed by the GOS score is known to correlate with sinus mucosal inflammation. Therefore, in cases of eCRS recurrence, osteitis of the paranasal sinuses is suspected to be involved.[5] Osteitic changes are often found even in non-operated patients.[14]

In CRS, there is a scoring system for osteitis called Global osteitis scoring (GOS), which has been

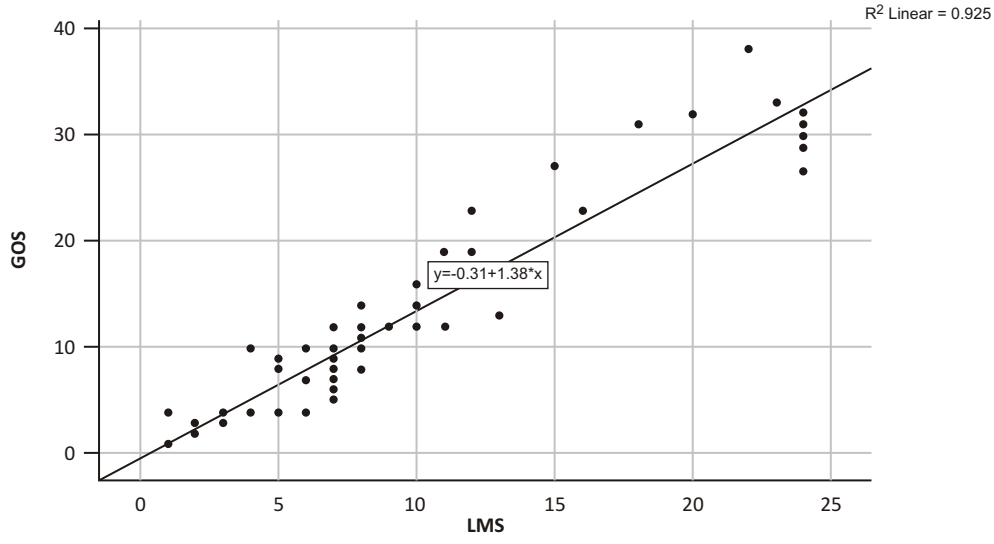

Figure 2. Correlation between Lund Mackay CT score (LMS) and Global Osteitis Score (GOS), Spearman test results with a *p value:* 0.05 and rho: 0.951

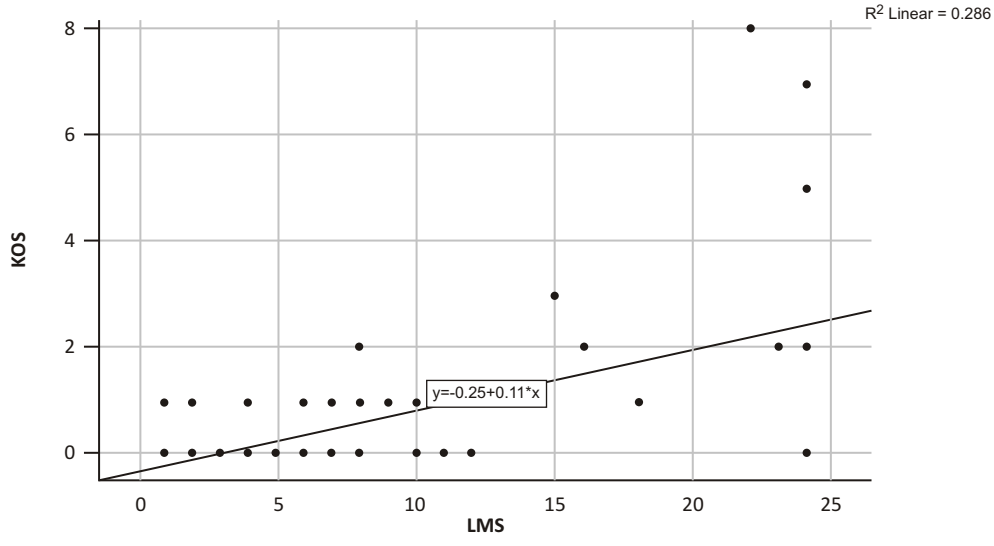

Figure 3. Correlation between Lund Mackay CT score (LMS) and Kennedy Osteitis Score (KOS), spearman test results with a *p value:* < 0.05 and rho: 0.450

investigated with cross-sectional RSK studies. The maximum score for sinus in GOS is achieved when the wall thickness is 5 mm or more.[15] Snivdong study showed the correlation between LMS and GOS of score 0 (p<0.001) and the correlation between LMS and KOS of score 0 (p<0.001). Kennedy Osteitis Score is positively correlated with CT score (p= 0.001). Our findings showed that LMS is significantly positively correlated with GOS and KOS (p *value* <0.05). Bone thickness assessment and osteitis grading in all 10 (right and left side of frontal, anterior ethmoid, posterior ethmoid, maxilla, and sphenoid) sinuses were conducted to improve assessment method. Kennedy Osteitis Score is not only a useful and easier tool but also highly reproducible by measuring the maximum thickness of sinus wall. Global Osteitis Score may be more complex for assessing severity (bone thickness) and extent of change but it may be potentially better for describing area involvement. A significant correlation was demonstrated between the two grading systems in this study. Chronic rhinosinusitis patients with osteitis reported more severe disease and less functional improvement.[16]

Osteitis severity in CRS can be determined using several methods. The most frequently used osteitis index is GOS and KOS index. We used LMS with GOS and LMS with KOS to assess osteitis severity. In comparison with

plain radiographs, CT scans can provide more detailed information regarding erosion and abnormalities of the bone structure of the paranasal sinuses; including bone thickness, sinus involvement, and the number of sinuses involved which is used for assessing osteitis severity using GOS and KOS.[17]

In this study we only analysed the severity of CRS using tomography computer with only single expertise, we did not analyse the disease severity with clinical features, endoscopy, and histopathological findings in our subjects. Further researches are needed to identify the correlation between osteitis grading and clinical features, endoscopy, and histopathological findings in chronic rhinosinusitis patients. It is imperative to conduct a systematic review and or meta-analysis to assess the correlation between Global Osteitis Score and Kennedy Osteitis Score; and chronic rhinosinusitis severity.

CONCLUSION

This study shows significant correlation between CRS severity assessment using LMS and bone thickening and remodelling assessment using GOS and KOS. LMS has a stronger positive correlation with GOS in comparison with KOS.

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Original Article

Risk Factors for Orbital Complication in Odontogenic Rhinosinusitis

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Abstract

Background : Orbital involvement is the most common complication in rhinosinusitis presenting about 60–75%. The manifestation of orbital complications such as eyelid edema, proptosis, eye movement disorder and loss of vision. The potential risk factors for developing complications are described in several studies. The purpose of this study was to examine the risk factors for orbital complication in odontogenic rhinosinusitis.
Methods : A retrospective case control study of 34 patients from July 2022 to July 2023 based on medical records. The subjects were classified into two groups, the case group involving odontogenic rhinosinusitis patients with orbital complication and the control group involving patients without orbital complications. Risk factors were sex, onset of odontogenic sinusitis, sinonasal symptoms, diabetes, histopathological findings, laboratory findings and CT scan images of sinus. The characteristics of orbital complications and the types of pathogenic bacteria cultivated were recorded.
Results : There number of patients in each group were 17, with the female to male ratio of 2,4:1, aged 8 to 81 years were enrolled in this study. The most common orbital complication was sub periosteal abscess (41%). We found 64% positive bacterial growth from tissue culture dominated by *Staphylococcus sp.* (54.5%). Histopathological examination showed the main inflammatory cell of the sinus mucosal epithelium was neutrophil in both groups. The logistic regression test showed that the risk factors for orbital complication were absolute neutrophil count *p* 0.008, OR 81.062, mucopurulent discharge p 0.009, OR 0.006 and sinus involvement *p* 0.027, OR 0.152.
Conclusion : Orbital complications were associated with sinus involvement with main symptom involving mucopurulent discharge and higher absolute neutrophil count.

Keywords : orbital complications, odontogenic rhinosinusitis, risk factor

INTRODUCTION

Odontogenic rhinosinusitis refers to bacterial maxillary sinusitis, with or without extension to other paranasal sinuses, secondary to either adjacent infectious maxillary dental pathology, or following complications from dental procedures. Odontogenic rhinosinusitis could account for 25% to 40% of all chronic maxillary sinusitis, and 45% to 75% of unilateral maxillary sinus opacification on computed tomography (CT) images.[1] The incidence of odontogenic rhinosinusitis in Indonesia is from 10% to 36%.[2]

Odontogenic rhinosinusitis may cause complications of orbital, intracranial, and osseus infections. These complications can occur ranging from acute rhinosinusitis (ARS) to chronic rhinosinusitis (CRS) and tend to be associated with ARS in pediatric patients and CRS in adult patients. Among the types of complication, 60% to 80% are orbital, 15% to 20% are intracranial, and 3% to 10% are bone complications.[3] A retrospectives study in Bucharest shows that during a five-year period, 25,48% odontogenic patients were admitted to the ENT department. Of the 517 patients with odontogenic sinusitis, 46 patients were diagnosed with occlusal-orbital complications (8,89%).[4]

Odontogenic infections usually gain access to the orbital cavity through the maxillary sinus, associated facial vasculature, deep temporal space, pterygopalatine fossa, and inferior orbital fissure. Orbital complications classified anatomically by the orbital septum include pre-septal cellulitis or abscess, post-septal (orbital) cellulitis, subperiosteal abscess, orbital abscess (intraconal), and cavernous sinus thrombosis.[5]

Regarding sinus treatment for complicated odontogenic sinusitis, only 50% of cases in the literature were treated with endoscopic sinus surgery (ESS), with external approaches being performed in 40% of cases.[3]

While odontogenic sinusitis diagnosis and management have been discussed in recent review or consensus articles, these have mainly focused on uncomplicated odontogenic sinusitis. Complicated odontogenic sinusitis is rarely described.

METHODS

This was a retrospective case-control study conducted on rhinosinusitis patients who were admitted to Kariadi General Hospital, a tertiary hospital in Central Java, Indonesia, between 2022 and 2023. The study population was odontogenic rhinosinusitis patients with and without orbital complications defined based on EPOS criteria and confirmed using computed tomography of sinuses and orbits. Exclusion criteria involved patients with a history of nasal or orbital surgery such as functional endoscopic sinus surgery (FESS), previous trauma or fractures to the orbit or nasal cavity, and known orbital anomalies, malignancy, dacryocystitis, or postoperative infection. This study has been approved by the Health Research Ethics Committee of Kariadi General Hospital.

The patient data were obtained from the electronic medical records of Kariadi General Hospital. The retrieved data included the diagnosis of odontogenic rhinosinusitis and informations regarding age, sex, onset of odontogenic sinusitis, sinonasal symptoms, concomitant diseases, microbiology culture, histopathological findings, laboratory findings and CT scan images of the sinus. The CT scan images were evaluated by radiologist who specializes in this field.

Orbital complications were evaluated using the Chandler's classification system, which categorizes types of orbital cellulitis into five different stages. These stages included (1) pre-septal cellulitis, (2) post-septal cellulitis (orbital cellulitis), (3) subperiosteal abscess, (4) orbital abscess, and (5) cavernous sinus thrombosis. The sample size of each group was calculated using the matched case control method, there were 17 subjects in each group.

We analyzed clinical and demographic data using descriptive statistics and IBM® SPSS® Statistics version 25. We used Fisher's exact test or chi-square test for categorical variables, the t test for comparisons of means, and the Mann-Whitney U test for nonparametric continuous variables. Spearman's correlation was used to assess associations between variables. We considered $p \leq 0.05$ to indicate statistical significance.

RESULTS

Thirty-four patients were included in the study. Female patients were more (70.6%) than males (29.4%) with the female to male ratio was 2,4:1. Patient age ranged from 8 to 80 years, with a mean ± SD of 42.5 ± 18.28 years. There were 4 (23%) patients aged <18 years, 10 (58%) patients aged 18 to 60 years and 3 (9%) patients with orbital complications. The presence of orbital complications was pre-septal cellulitis (2 patients), orbital cellulitis (6 patients), subperiosteal abscess (7 patients), orbital abscess (2 patients) and cavernous sinus thrombosis (1 patient). Clinical symptoms for orbital complications were mostly edema (82%), hyperemia (59%), pain (59%), visual impairment (52%), ptosis (35%), and ophthalmoplegia (18%). The correlation between case and control groups are summarized in Table 1.

Microbiological examination was only performed on the case group, showing that 64% of patients had positive bacterial growth from tissue culture, consisting of gram-positive bacteria (32.3%) and gram-negative bacteria (14.7%). The results of bacterial culture were *Staphylococcus sp*. (54.5%), *Peptostreptococcus sp*, *Streptococcus sp*, *Burkholderia cepacia*, *Enterobacter cloacae*, and *Pediococcus pentasaceus*. We also found fungi in 2 cases, *Candida cifferrii* and *Mucor Sp*.

TABLE 1
The correlation between case and control groups

Variables		Groups				*p*	OR (95% CI)
		Case		Control			
		n	%	n	%		
Sex	Male	7	41.2	8	47.1	1.000[α]	0.89 (0.45 – 1.77)
	Female	10	58.8	9	52.9		
Leukocyte	Leukocytosis	10	58.8	4	23.5	0.081[α]	2.04 (1.03 – 4.04)
	Normal	7	41.2	13	76.5		
ANC	>7000	10	58.8	3	17.6	0.034[α*]	2.31 (1.18 – 4.53)
	≤7000	7	41.2	14	82.4		
Sinusitis	Maxilla	15	88.2	17	100	0.242[b]	0.45 (0.32 – 0.68)
	Ethmoid	16	94.1	12	70.6	0.087[b]	3.43 (0.56 – 21.11)
	Frontal	8	47.1	5	29.4	0.480[α]	1.44 (0.75 – 2.76)
	Sphenoid	8	47.1	2	11.8	0.060[α]	2.13 (1.17 – 3.90)
Sinus involvement	Maxilla	1	5.9	5	29.4	0.046[c*]	–
	Maxilla + ethmoida	5	29.4	5	29.4		
	Maxilla+ethmoida+frontal/sphenoid	8	47.1	7	41.2		
	Pansinusitis	3	17.6	0	0		
Onset	<12 weeks	3	17.6	2	11.8	0.500[b]	1.24 (0.55 – 2.79)
	≥12 weeks	14	82.4	15	88.2		
Tissue inflammatory	Neutrophyls	15	88.2	13	76.5	0.328[b]	1.61 (0.49 – 5.25)
	Eosinophyls	2	11.8	4	23.5		
Symptoms	Nasal obstruction	11	64.7	13	76.5	0.707[α]	0.76 (0.39 – 1.49)
	Mucopurulent discharge	7	41.2	15	88.2	0.012[α*]	0.38 (0.20 – 0.74)
	Anosmia	5	29.4	5	29.4	1.000[α]	1.00 (0.45 – 2.09)
	Facial pain	13	76.5	12	70.6	0.005[α*]	1.17 (0.51 – 2.66)
Comorbid	Diabetes	6	35.3	4	23.5	0.707[α]	1.31 (0.67 – 2.55)

ANC: Absolute neutrophil count. Statistical analysis a Continuity Correction, [b] Fisher's exact, [c] Mann-Whitney*p<0.05 significance

The onset of odontogenic rhinosinusitis in both groups were mostly more than 12 weeks, and categorized as chronic rhinosinusitis. The main symptom of odontogenic rhinosinusitis was facial pain, followed by nasal congestion, mucopurulent discharge and anosmia. Only mucopurulent discharge has significance correlation with orbital complication, with mild odd ratio.

Histopathological examination showed neutrophils as the main inflammatory cell of the sinus mucosa, both in the case (88.2%) and control (76.5%) groups. In both groups, diabetes was not dominance and there was no significant difference between two groups.

Computerized tomography of the paranasal sinus showed the predominance of sinus opacities in the maxillary and ethmoid sinuses in both case and control groups. However, statistical analysis showed no significant correlation with orbital complications. We classified the severity of the paranasal sinus involvement based on tomography computer, showing that the involvement of three sinuses (either combination of maxilla, ethmoid and frontal or maxilla, ethmoid and sphenoid sinuses) was the most common in both case and control groups. Pansinusitis was only found in case group. There was a significant correlation in statistical analysis.

TABLE 2
The risk factors for orbital complications in odontogenic rhinosinusitis

Variables	*p*	OR	95% CI
Leucocytosis	0.460	3.736	0,113 – 123,585
ANC	0.008*	81.062	3,156 – 2081,933
Ethmoid sinus	0.473	0.173	0,001 – 20,923
Sinus involvement	0.027*	0.152	0,029 – 0,804
Mucopurulent discharge	0.009*	0.006	0,000 – 0,280

*p<0.05 significance

The laboratory findings show that leukocytosis was most common in the case group. There was no significant correlation between leukocytosis and orbital complications. The absolute neutrophil count in case group was higher than in the control group, and there was a significant correlation with orbital complications.

The logistic regression test showed that ANC, sinus involvement and mucopurulent discharge had a *p value* <0.05. It can be concluded that ANC, sinus involvement and mucopurulent discharge were the dominant factors influencing the orbital complication.

DISCUSSION

Odontogenic sinusitis is one of the most common causes of unilateral sinus diseases, and certain odontogenic bacteria are more common in odontogenic sinusitis than in rhinosinusitis, previous studies of rhinosinusitis complications could have overlooked odontogenic sinusitis as a cause of orbital complications. Complicated odontogenic sinusitis affected all ages and sexes in this study.

Odontogenic sinusitis is usually found in patients aged between 40 and 60 years and has predominance in female compared to male, with a ratio of 1:1.33 in previous studies.[6] The mean age of subjects was 42.5 years and female was more frequent than male, thus consistent with previously published data reporting an older mean age. Previous studies have reported orbital and intracranial complications due to rhinosinusitis mostly in a pediatric population due to imperfect bone growth and open cranial sutures as predilection sites for the spread inflammation.[7,8] However, in retrospective study in Taiwan showed no significant difference of orbital complication in children (42.2%) and adults (57.8%) patients.[9] The orbital complications were reported in 44,1% of invasive fungal rhinosinusitis in adult population, and were higher in female than male (61% : 39%).[10] A retrospective study in Bucharest shows that the orbital complications in adult odontogenic sinusitis mostly occurred in elderly (44,4%).[11] The subjects of our study were odontogenic rhinosinusitis, a rare condition in pediatric.[12] Some studies reported that odontogenic sinusitis was usually found in patients aged between 40 and 60 years old and was slightly more frequent in women: 57.7% than men 42.82%, with a ratio of 1:1,33.[6] This is in line with our study showing that our subjects mostly aged 18 to 60 years.

The onset of odontogenic sinusitis in our study was mostly more than 12 weeks in both groups. Odontogenic sinusitis can be classified as acute and chronic, in which the predominance symptoms in acute phase are fever, headache and suborbital pain. It can be developed into chronic if disease is unrecognized nor controlled. Most odontogenic sinusitis is in chronic condition as many patients are not aware of the symptoms of sinusitis.[13] Patients with acute condition was found in children and young adults. The rate of complications varies from 3% to 20% in patients hospitalized with ABRS.[14]

Sinonasal symptoms of odontogenic sinusitis were unilateral and consistent with cardinal symptoms of rhinosinusitis such as nasal congestion, anterior or posterior nasal discharge, facial pain and anosmia or hyposmia.[15] Other symptoms include purulent discharge in the oral cavity and dental pain.[16] In acute phase, the predominance symptoms are foul odor, and head or facial pain. The cardinal symptoms in chronic odontogenic sinusitis are malodorous scent with unilateral facial pressure, that is confirmed by the presence of pus in the middle meatal, mucosal swelling or protrusion of uncinate process and opacification of the unilateral sinus in computed tomography images. Unilateral maxillary sinusitis could be related to dental pathology and odontogenic sinusitis was found in 45–72% of unilateral maxillary opacification in computed tomography images.[13] In our study, mucopurulent discharge was the only symptom significantly correlated with orbital complications.

The main complain of orbital complications was edema (82%), while the other symptoms were hyperemic (59%), pain (59%), visual impairment (52%), ptosis (35%), and ophthalmoplegia (18%). This result is consistent with a systematic review reporting three most frequently

symptoms found in literature involving periorbital edema (100%), ocular or facial pain (82.9%) and limited ocular movements (82.9%).[17] Our study showed the most common orbital complication involving subperiosteal abscess and orbital cellulitis. This result is similar with previous study examining odontogenic orbital cellulitis, reporting that the two most frequent types found in the literature corresponded to an intra-orbital abscess (Chandler stage IV) (42.9% of cases) and subperiosteal abscess (Chandler stage III) (25.7% of cases).[17] Other study shows the three most frequent symptoms involving subperiosteal abscess (22%), post-septal cellulitis (14%) and orbital abscess (8%).[3] In contrast to previous study, it was reported that pre septal cellulitis was the most common orbital complication,[4] and severe complications can occurred in older patients or delay in hospitalization.[18]

Odontogenic sinusitis is a polymicrobial infection in which bacteria, predominanly anaerobic species, from both oral cavity and upper respiratory system are involved. Anaerobic bacteriological flora is the most common cause of chronic OMS, while the main flora is mixed in patients with acute OMS.[19] An interesting finding was the fact that although we collected samples for bacteriological examination from sinus and orbital secretions at admission and during surgery, the laboratory did not find pathogens from 6 to 17 cases (34%). This may be related to the use of broad-spectrum antibiotic therapy at diagnosis and prior to sampling. In 64% of positive-bacterial growth from tissue culture, we found 32.3% of gram-positive bacteria and 14.7% of gram-negative bacteria.

The microbiological results in this study shows the most common germs were *Streptococcus sp*. (17.6% of cases) and *Staphylococcus sp*. (5.8% of cases). Similar results from previous study shows the most common germs found are commensal streptococcus of the oral cavity or anaerobic bacteria (25.7% of cases), and coagulase-negative staphylococcus (22.9% of cases).[17] The microbiological findings in acute odontogenic sinusitis showed aerobic bacteria such as *Hemolytic Streptococcus alpha*, *microaerophilic streptococci*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, and also anaerobes such as Gram-negative bacilli, *Pepto-streptococcus*, *Fusobacterium sporulatum*, and *Propionibacterium acnes*. The most frequent germs of chronic odontogenic sinusitis are anaerobes such as Gram-negative bacilli, *Pepto-streptococcus*, and *Fusobacterium spp*., while aerobes can also be encountered in some cases, such as *Streptococcus c. alpha-hemolytic*, *Streptococcus c. microhemolytic*, *Staphylococcus aureus*.[6] Chronic odontogenic sinusitis is strongly associated with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenza* and *Moraxella catarrhalis*.[20]

Tissue inflammation from nasal mucosal biopsy was dominated by neutrophilic inflammation, either in case (51.9%) and control group (48.1%). It may be because of the mucosal inflammation in odontogenic sinusitis due to by bacterial infection. Severe periodontal disease can lead to inflammation of the maxillary mucosa and ultimately odontogenic sinusitis. This is due to a significant increase in pathogenic bacteria, by-products and inflammatory cytokines which reach the sinus mucosa directly through diffusion or indirectly through the lymph vessels, resulting in inflammation of the sinus mucosa. One of the causes of odontogenic sinusitis is endodontic infection, where bacterial invasion occurs in the pulp chamber and root apex developing into an inflammation or infection in the apical periodontium known as apical periodontitis.[20]

The extents of sinus opacities are mostly in involved maxilla, ethmoid and either frontal or sphenoid sinuses, and similar in both groups. Previous retrospective studies assessing paranasal sinus involvement in rhinosinusitis reported an equal involvement of frontal, maxillary and ethmoid sinuses in rhinosinusitis patients with orbital and intracranial complications, while others found no difference among all paranasal sinuses.[7] However, in comparison with rhinogenic rhinosinusitis, the involvement of the posterior ethmoid sinus and sphenoid sinusitis is rare in odontogenic sinusitis.[21] In our study, the involvement of paranasal sinuses were statistically significant with orbital complications. The computed tomography scan images show pansinusitis only found in groups with orbital complication. Due to its posterior location, sphenoid sinusitis can spread directly to the posterior orbit and cause orbital apex syndrome without first going through the classic stages of orbital complications. Patients with deterioration of vision and worsening ophthalmoplegia are candidates for immediate spheno-ethmoidectomy and optic nerve decompression. This procedure can be combined with orbital decompression if the patient manifests increased intraocular pressure.[3]

Our study found that diabetes mellitus was not a significant risk factor for orbital complication. This is different with common studies. Patients with comorbid or underlying conditions, such as diabetes and chronic renal failure with impaired immune function may have higher risk for orbital complications.[5] Similar with orbital complications, systemic diseases are the risk factors for odontogenic sinusitis, such as diabetes mellitus and immunodeficiency. This is thought to be due to the inability of the immune system to resist infection or the difference in the type of pathogens involved in the infection. People with systemic diseases also have a higher risk of complications, higher mortality, and a longer hospital stay.[16]

Leukocytosis was recorded in 14 patients, in which 10 patients experienced orbital complication while 4 patients did not. The assessment of absolute neutrophil count showed a higher ANC count (>7000 cells/mL) in

13 patients. In current series, most patients presenting with orbital complications of acute rhinosinusitis have elevated leukocyte and ANC counts.[22] Experimental studies have demonstrated that neutrophil-mediated abscess formation is a relevant component of innate immune response which aids host defense against skin infections, inhibiting the spread of pathogens to deeper tissues.[22] Raised leucocyte count as well as left shift (an increase in the number of immature leucocytes in the peripheral blood, particularly neutrophil band cells) have been reported as strongly associated with (subperiosteal or intraorbital) abscess formation. In our study we found that higher absolute neutrophil count was associated with orbital complication in odontogenic rhinosinusitis.

The limitation of this study is we did not analyze other risk factors for orbital complications such as biofilm factor, immunocompromised and other chronic diseases. For further study, we recommend to analyze all of the risk factors.

CONCLUSION

Orbital complications in odontogenic sinusitis were associated with mucopurulent discharge, absolute neutrophil count and sinus involvement. A thorough history taking and clinical examination along with laboratory examination and radiological evaluation is mandatory in patients with suspected complications. Treatment requires multidisciplinary collaboration between otorhinolaryngologist, ophthalmologist and dental surgeon. Larger studies will be necessary to assess the correlation of complications of odontogenic rhinosinusitis.

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Case Report

A 25-year-old Woman with Cholecystolithiasis, Cholecystitis, Choledocholithiasis, and Acute Hepatitis

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Abstract

Background : Gallstone disease stands as the foremost gastrointestinal issue leading to hospital admissions, while also emerging as a substantial global public health concern, impacting approximately one-fifth of the population.
Case Report : A 25-year-old woman was admitted with abdominal pain with a history of gallstones. She had risk factors such as obesity with a Body Mass Index (BMI) of 35.3 and dyslipidemia. Further examination showed that she had acute hepatitis and choledocholithiasis. The patient underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) with balloon extraction. The patient recovered from her condition then scheduled for cholecystectomy.
Conclusion : This case showed a relatively young female with cholecystolithiasis, cholecystitis, choledocholithiasis, and acute hepatitis presenting with colicky pain. Comprehensive management of gallstone diseases is essential to avert additional complications and the possibility of relapse, especially considering the young age of the patient.

Keywords : Cholecystolithiasis, Cholecystitis, Choledocholithiasis, Fatty liver

INTRODUCTION

Gallstones and cholelithiasis are common gastrointestinal problems in Europe, the USA, and other developed countries.[1–3] Gallstone disease has strong links with metabolic disorders such as obesity, dyslipidaemia, and type 2 diabetes, which also has a high prevalence.[1–3] The majority of people who have gallstones remain asymptomatic.[1–3] But gallstones can obstruct the cystic duct thus making the gallbladder distended.[1–3] Prolonged obstruction results in inflammation and infection of the gallbladder or the cystic duct, and even ischemia.[1–4] Repeated inflammation can result in chronic cholecystitis.[3,4] In this case, showed a comprehensive management of gallstone disease that is needed to prevent further complication that could be done currently in hospital in Central Java, Indonesia.

CASE REPORT

A 25-year-old woman was admitted to Emergency Room at Kariadi General Hospital with abdominal pain as the chief complaint. She felt abdominal pain especially in the epigastric and upper right quadrant 2 days before going to the emergency room. She felt the pain like being stabbed with a needle. The pain was not radiated into the shoulder or jaw. She felt the pain was constant and not influenced by activity. The patient also felt the pain worsen 5 hours before admission to the emergency room. The patient consumed over-the-counter pain medicine s but the pain persisted even though she consumed multiple over-the-counter pain drugs. The patient is also nauseated, vomiting, and perspiring.

The patient had a history of gallstones one year ago, from an ultrasound examination. The patient underwent an abdominal ultrasound examination one year ago due to abdominal pain that was like the current pain but milder. However, the patient never felt the pain again until 2 days before going to the emergency room, so the patient never followed up nor took any medications for the gallstone. The patient had not checked her lipid profile or her blood glucose levels. She worked as a cashier in Semarang City. She had no history of consuming alcohol.

In the emergency room, the patient's blood pressure was 120/80, the pulse rate was 96, the respiratory rate was 20, the temperature was 36.2°C, and the oxygen saturation was 99% room air. The visual

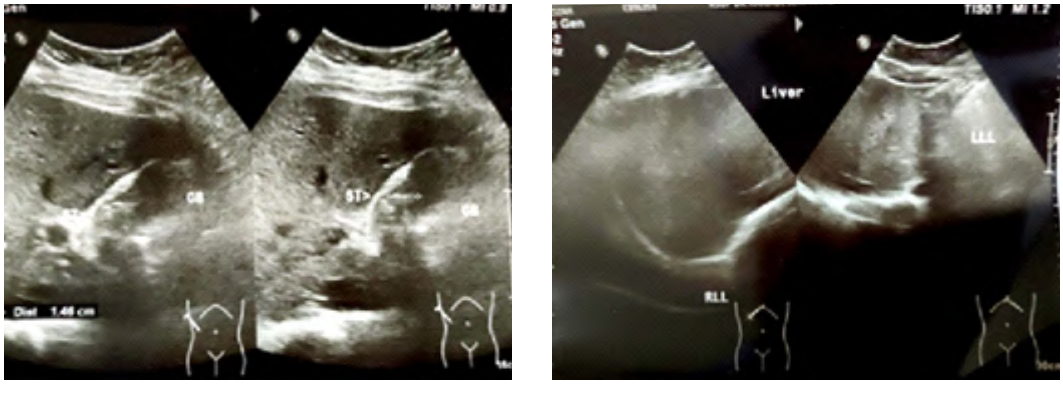

Figure 1. An abdominal ultrasound examination showed a grade II fatty liver and multiple cholecystolithiasis.

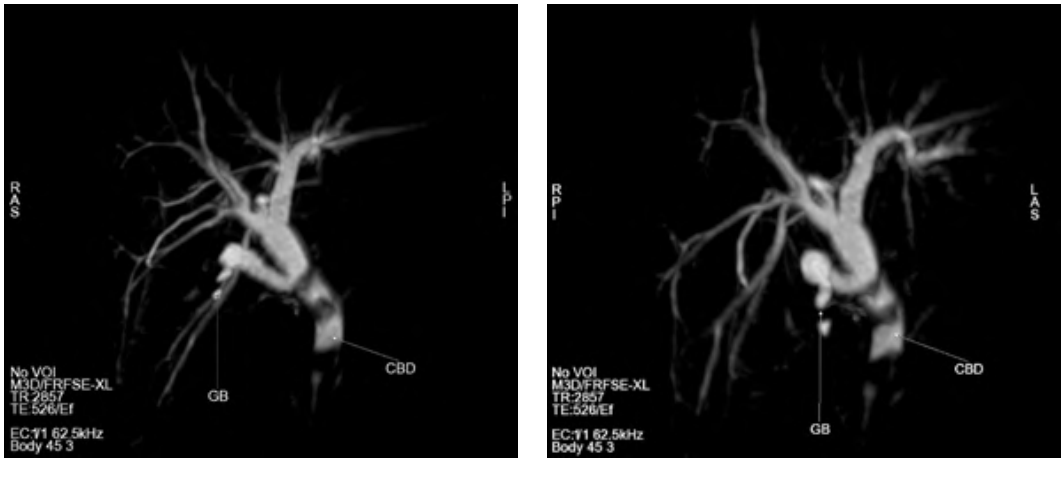

Figure 2. MRCP showed a widening of the intrahepatic and extrahepatic bile ducts.

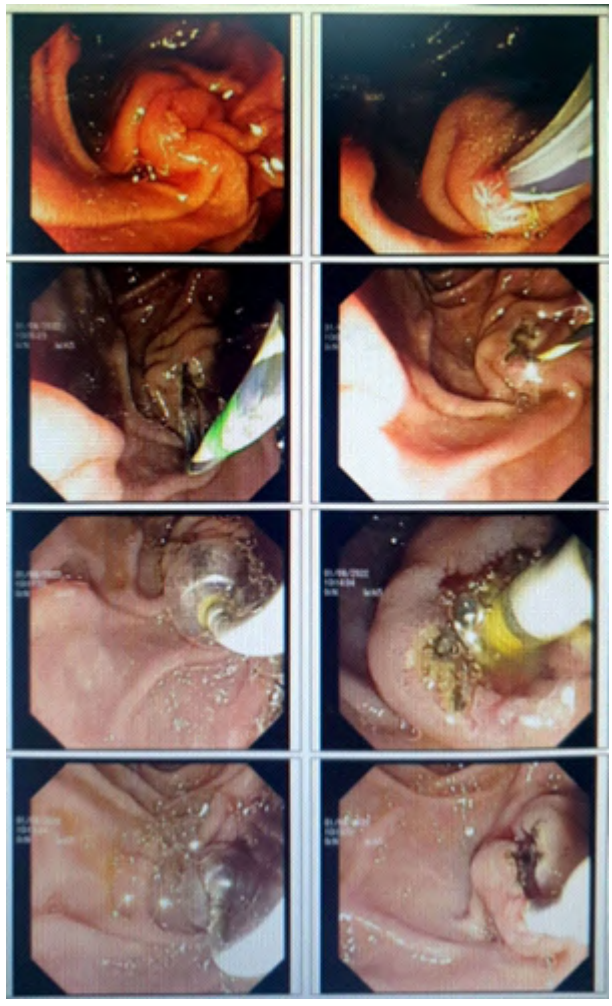

Figure 3. ERCP showed sludge in the common bile duct. Balloon extraction was performed.

analogue scale for abdominal pain is 6–7. The physical examination showed abdominal tenderness in the epigastric and upper right quadrant with positive Murphy's sign. The liver and spleen were not palpable. The patient was obese with a 95kg weight, 164cm height, and Body Mass Index (BMI) of 35.3. Then the patient was admitted to inpatient care and given ketorolac, metoclopramide, and hyoscine intravenously.

The patient undertook a laboratory examination. The patient had leucocytosis with leukocytes 14.700. The patient also had elevated liver function test parameters. The Aspartate Aminotransferase (AST) was 748 U/L, the Alanine Aminotransferase (ALT) was 545 U/L, the Alkaline Phosphatase was 151 U/L, and the Gamma GT was 488 U/L. We calculated the r-factor to differentiate between cholestatic and hepatocellular injury, and it was 8.2, which is consistent with a hepatocellular injury pattern. The total bilirubin was 2.92 mg/dL with direct bilirubin 1.95 mg/dL and indirect bilirubin 0.97 mg/dL. The albumin and globulin were normal.

Because the laboratory showed hepatocellular injury, the patient was tested with immunoserology tests, and the HBsAg, anti-HCV, and IgM anti-HAV were all negative. The patient was also scheduled for an abdominal ultrasound examination.

On the second day of inpatient care, the pain persisted. The patient was given ampicillin-sulbactam 1.5 grams three times intravenously and ursodeoxycholic acid twice daily.

From the ultrasound examination, there was a grade II fatty liver without widening of the portal vein. The intrahepatic and extrahepatic bile ducts were normal. There was also multiple cholecystolithiasis (maximum size was 1.46cm). The spleen size was normal, and the splenic vein was not widened.

The patient was also tested for a urinalysis and lipid profile. The urinalysis findings were normal. The total cholesterol was 174, triglyceride was 200, HDL cholesterol was 22, and direct LDL was 79.

On the fourth day of inpatient care, the third day of

antibiotics given, the symptoms decreased significantly. The patient was not vomiting, and the pain was reduced significantly. Then, the patient was programmed for Magnetic Resonance Cholangiopancreatography (MRCP) to find any stone in the bile duct.

From the MRCP, there were multiple filling defects on the distal common bile duct (maximum size was 1.4x1.1cm), and multiple filling defects in the vesica velea (maximum size was 1.1x1.0cm). There was also a widening of the right hepatic duct (0.8cm diameter), left hepatic duct (0.7cm diameter), common hepatic duct (1.4cm diameter), and common bile duct (1.2cm diameter). There was no widening of the pancreatic duct. It also showed the gallbladder was in normal size with thickening of its wall.

The liver function test was evaluated on the fifth day of inpatient care. The AST was 38 U/L, the ALT was 184, the ALP was 126, and the GGT was 55. The total bilirubin was 1.9 mg/dL with direct bilirubin at 1.3 mg/dL and indirect bilirubin at 0.6.

On the eighth day of inpatient care, the patient underwent *Endoscopic Retrograde Cholangiopancreatography* (ERCP). The mucosa of the ampulla was not oedematous and hyperaemic. There was no tumour or mass. There was bile surrounding the mucosa. Cannulation was performed, and a guide wire was entered. When the contrast entered, the common bile duct was widened, and a filling defect on the distal common bile duct. Sphincterotomy was performed, followed by sweeping with a balloon extractor multiple times, and the sludge came out without stone.

On the ninth day of inpatient care, one day after ERCP, the pain was gone, and the patient was not vomiting. The patient was discharged.

Ten days after discharge, the patient went to the outpatient clinic and was tested with a liver function test. The test came out normal. The AST was 11 U/L, the ALT was 16 U/L, the Alkaline Phosphatase (ALP) was 77 U/L, the Gamma-GT (GGT) was 60 U/L, and the total bilirubin was 0.9. The resulting culture from bile acid was Proteus vulgaris, sensitive to ampicillin-sulbactam which was given intravenously during the outpatient stay. She did not feel any abdominal pain or vomiting. The patient was given ursodeoxycholic acid twice daily and was educated to lose weight and avoid food with high cholesterol and saturated fats. To prevent further complications, the patient was then scheduled for cholecystectomy.

DISCUSSION

Advanced age, female sex, a diet high in carbohydrates and low in fiber, obesity, and genetic factors are all risk factors for gallstone disease. This patient, although relatively young age, is obese with a BMI of 35. Obesity will activate the pathogenic pathways that lead to gallstone formation, including abnormal gallbladder emptying, increased cholesterol crystallization tendency, stone aggregation, and supersaturation of bile with cholesterol. Gallstones that include pigment reveal problems with bilirubin metabolism.[1–3]

Gallstone prevention includes frequent, healthful activity, a nutritious diet, and maintaining a normal body weight. Additionally, ursodeoxycholic acid aids in preventing the growth of cholesterol crystals in bile. A diet high in vitamin C or regular vitamin C supplementation (500 mg 4 times per day) may prevent gallstone development.[1–3]

Gallstones may go undiscovered or discovered accidentally in asymptomatic patients or produce colicky pain as complications emerge. The characteristic of colicky pain is episodic attacks of severe pain in the right upper abdominal quadrant of the epigastrium for at least 15–30 minutes with radiation to the right back or shoulder and a positive reaction to analgesics. Laboratory tests from uncomplicated symptomatic gallbladder stones are within normal values in most patients. Diagnosis can be achieved from abdominal ultrasonography to *computed tomography* (CT), *magnetic resonance cholangiopancreatography* (MRCP), and cholecystography.[1–3]

Acute cholecystitis is the most common complication of gallstones, occurring in about 10% of the patients with symptomatic gallstones, and represents one-third of all surgical emergency hospital admissions. The stones obstruct the cystic duct thus causing inflammation.[1,2]

Acute cholecystitis symptoms include strong pain that gets worse with time and radiates to the right shoulder or interscapular region. These symptoms are frequently accompanied by fever, nausea, and vomiting. Murphy's sign, which manifests as pain in the right upper abdominal quadrant and tenderness on palpation (but not the left), is a highly sensitive and specific diagnostic indicator. White blood cell counts and C-reactive protein levels are frequently elevated. Gallstones, a swollen gallbladder, a thicker (>4mm) gallbladder wall, and pericholecystic fluid can all be found with abdominal ultrasound, and sonographic Murphy's sign (intensified pain upon probe pressure directly over the gallbladder) may be present.[1,4,5]

Ursodeoxycholic acid should only be used to treat symptomatic patients who have tiny stones that are known to have originated from gallbladder sludge or cholesterol. Every time, the patient should be made aware of the possibility of a curative cholecystectomy in advance. Nonsteroidal anti-inflammatory drugs are the best therapy option for biliary colic. In addition to adding spasmolytics (e.g. butyl scopolamine), opioids such as buprenorphine may be utilized if the pain is exceptionally bad. Buprenorphine is best suited because it appears to contract the sphincter Oddi less than morphine. Empirical antibiotics must be given right away

in cases of acute cholecystitis with symptoms of sepsis, cholangitis, abscess, or perforation.[1,3]

Given that almost half of patients with symptomatic cholecystolithiasis experience recurrent colic, cholecystectomy may be necessary depending on the frequency and severity of symptomatic episodes. Bile acid dissolution therapy with *Ursodeoxycholic Acid* (UDCA) and *Extracorporeal Shock Wave Lithotripsy* (ESWL) is one of the alternatives to surgery, although these treatments have a poor rate of cure, high risk of gallstone recurrence, and ineffectiveness in reducing symptoms and consequences following medical treatment. In carefully chosen individuals, the cure rate for gallstones is only 27% after UDCA and only 55% after ESWL, and the recurrence rate was >40% following complete stone disintegration or ESWL for 4 years.[1,4,5]

Although cholecystectomy is the preferred course of treatment, the advantages of surgery for acute calculous cholecystitis have never been well investigated. While doing a cholecystectomy in the event of acute cholecystitis reduces further bouts of gallstone-related disease, it is important to be aware of the relatively high complication rate, especially in high-risk individuals. Therefore, it is important to carefully explore your options before having surgery. However, leaving the gallbladder in place runs the risk of causing recurring gallstone-related illness.[6]

Loozen *et al* (2016) said, in their research from 1841 patients in randomized controlled trials and 14 non-randomized studies, that conservative treatment of acute cholecystitis seems feasible and safe, especially in patients with mild disease. And less than 25% of the patients appear to experience recurrent gallstone-related illness during long-term follow-up without surgery.[6]

In this case, the patient came with severe abdominal pain that persisted after the administration of nonsteroidal anti-inflammatory drugs and spasmolytics. Positive Murphy's sign and elevated white blood cell count were present. MRCP also showed a thickening of the gallbladder wall. So, the patient has acute cholecystitis due to cholecystolithiasis. After several days of antibiotics and symptomatic treatments, the symptoms were reduced significantly.[1,7,8]

As many as 3–16% of patients with gallbladder stones also have *Common Bile Duct* (CBD) stones, depending on their age. They either migrate from the gallbladder (secondary stones) or less frequently grow from scratch in the bile duct, as in the case of CBD dilatation with stasis (primary stones). Acute biliary discomfort, induced by CBD distention following partial or total obstruction, is a common sign of CBD stones. It might be difficult to distinguish the pain from the pain caused by gallbladder stones.[1,7,8]

Patients with symptomatic CBD stones may have altered liver biochemical tests, such as elevated serum bilirubin concentrations, as well as ALT, AST, gamma-GT, and ALP.[1,7]

Abdominal ultrasound has a high sensitivity for detecting CBD dilatation, which is an indirect indicator of CBD stones. Even in dilated CBD, stones may be seen clearly in ultrasound examination. CBD stones larger than 5 mm can be found with EUS and MRCP in patients who may have CBD stones but with an inconclusive abdominal ultrasound. For detecting CBD dilation, CT imaging is also highly sensitive. It also evaluates other possible causes of upper abdominal pain and gallstone complications. And lastly, ERCP has a very high sensitivity for detecting CBD stones.[1,7–9]

Although there may be a spontaneous passage to the small bowel in many cases, there is a high chance of biliary discomfort and related issues such as pancreatitis, cholangitis, and jaundice. Therefore, it is generally agreed that symptomatic choledocholithiasis should be treated. Endoscopic sphincterotomy and stone removal are currently the preferred approaches in most countries.[1,7–9]

In a condition where gallbladder stones and bile duct stones occur simultaneously, current studies show that laparoscopic cholecystectomy is recommended within 72 hours after ERCP and leads to significantly fewer recurrent biliary events as compared to delayed laparoscopic cholecystectomy (after 6–8 weeks). Cholecystectomy and ERCP are not recommended to be performed on the same day.[1]

This patient also had acute hepatitis with a marked increase in transaminase levels. The AST was 748 U/L, the ALT was 545 U/L, the Alkaline Phosphatase was 151 U/L, and the Gamma GT was 488 U/L. Examination of hepatitis A, hepatitis B, and hepatitis C were all negative. The patient had a history of taking over-the-counter pain medication due to abdominal pain, and the transaminase levels came back to normal after cessation of the drug, which may indicate drug-induced liver injury. The patient also had a fatty liver in the abdominal ultrasound, which may cause elevated transaminase levels. The patient is also obese, which is also a risk factor for developing inflammation easier than non-obese patients, due to the build-up of pro-inflammatory cytokines, such as TNF-α.

There are two types of drug-induced liver injury (DILI). Intrinsic DILI is typically dose-related and occurs in a large proportion of individuals exposed to the drug (predictable) and onset is within a short period (hours to days). Idiosyncratic DILI is usually not dose-related, occurs in only a small proportion of exposed individuals (unpredictable), and exhibits a variable latency to onset of days to weeks. DILI is diagnosed by one of the following thresholds: i) ≥ 5x Upper Limit Normal (ULN) elevation in ALT, ii) ≥ 2 x ULN elevation in ALP (particularly with accompanying elevations in concentrations of gamma-glutamyl transferase (GGT) in the absence of known bone pathology driving the rise in ALP level), or iii) ≥ 3 x ULN elevation in ALT and simultaneous elevation of bilirubin

concentration exceeding 2 x ULN. However, diagnosis of DILI has to be done after excluding other causes of liver injury, such as autoimmune hepatitis.[10,11]

A recent systematic review and meta-analysis of the prevalence of metabolic-associated fatty liver disease in the Asia-Pacific region is 29.62%. Obesity is the most common risk factor for fatty liver. Type 2 diabetes mellitus, high serum triglycerides, and low serum high-density lipoprotein (HDL) levels are also common in patients with fatty liver.[12,13]

This patient had hepatic steatosis detected by abdominal ultrasound, obesity (BMI of 35.3), high triglycerides (200), and low LDL (22). Therefore, the patients need further examination for advanced fibrosis risk assessment. Using transaminase levels in inpatient care, the patient's FIB-4 score was normal, therefore it is best to repeat non-invasive tests at an interval of 2–3 years. If there is an intermediate or high risk, liver biopsy or imaging may be done to assess the fibrosis stage or disease activity. Therapeutic options for fatty liver include lifestyle modification and exercise, metabolic risk management (e.g. dyslipidaemia, hypertension), and drugs such as pioglitazone or vitamin E. If the patient develops cirrhosis, management of cirrhosis must be done, including varices screening and treatment, HCC surveillance, or liver transplantation if indicated and feasible.[12,13]

CONCLUSION

Gallstones are common gastrointestinal problems and have strong links with metabolic disorders such as obesity and dyslipidaemia. This case showed a relatively young female with symptomatic cholelithiasis and choledocholithiasis with colicky pain. Gallstones may lead to cholecystitis, cholangitis, or even pancreatitis. Metabolic disorders also link with the fatty liver which may later cause liver fibrosis and liver failure. This patient's biggest risk factor is obesity with metabolic syndrome. Elaborate management of metabolic syndrome since adolescence is needed to prevent many diseases, like gallstones and their complications.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. Informed Consent was acquired from the patient.

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Case Report

Catastrophic Event Following Percutaneus Coronary Intervention Developing In-Stent Thrombosis Leading Massive Pericardial Effusion and Free Wall Rupture

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Abstract

Background : One extremely unusual but serious side effect of an acute myocardial infarction is left ventricular free wall rupture. It was reported to happen either during the sub-acute phase with overt cardiac remodeling (type III, 45%) or early after the beginning of Myocardial Infarction (MI) (type I or II, about 55%). Large infarct sizes, female gender, and advanced age have all been linked to an increased risk of free wall rupture. Clinicians continue to face significant challenges in diagnosing and treating this condition because of the diverse clinical manifestations linked to elevated death rates. This case report aims to highlight a rare occurrence of mechanical complication of acute myocardial infarction
Case : A 69-year-old male patient was referred because of chest pain and dyspneu. He had a primary Percutaneous Coronary Intervention (PCI) and was diagnosed with posterior ST-Evelation Myocardial Infarction (STEMI). The patient had a stent inserted into his ostial-distal Left Circumflex (LCx) artery. Three weeks later, a reangiography revealed a left ventricle (LV) aneurysm and stent thrombosis. Massive pericardial effusion with free wall rupture was seen on the echo. He was breathing heavily while in our emergency room. His blood pressure was 125/74 (94) heart rate was 94 bpm respiratory rate 24 times/minute, SpO2 was 98%, there were no rales, and his ankles had pitting edema. By the bedside, Echo revealed an LV aneurysm, a large, localized pericardial effusion without tamponade, and a possible free wall rupture. Later, he was taken to the intensive care unit and had heart surgery
Discussion : Complications from an acute myocardial infarction may be ischemic, mechanical, arrhythmic, embolic, or inflammatory. Significant short-term clinical improvement and long-term survival are linked to the emergence of mechanical problems following acute myocardial infarction.
Conclusion : The fact that primary Percutaneous Coronary Intervention (PCI) has significantly reduced the prevalence of this deadly event. Our results indicate that one of the key predictors and primary causes of this problem is a longer symptom of angiography time.

Keywords : Percutaneus Coronary Intervention, In-Stent Thrombosis, Massive Pericardial Effusion, Free Wall Rupture

INTRODUCTION

An uncommon but serious side effect of acute myocardial infarction (AMI) is left ventricular free wall rupture (LVFWR). It was observed to happen either during the sub-acute phase with overt cardiac remodeling (type III, 45%) or early after the beginning of Myocardial Infarction (type I or II, about 55%). Large infarct sizes, female gender, and advanced age have all been linked to an increased risk of free wall rupture. Especially, the diverse clinical manifestations linked to elevated mortality rates continue to provide a significant diagnostic and treatment obstacle for medical professionals.[1]

The aim of this study is to highlight a rare occurrence of a mechanical complication of acute myocardial infarction, specifically focusing on left ventricular free-wall rupture. Provide insights into the clinical manifestations, diagnostic challenges, and treatment strategies associated with this serious complication. Additionally, the study discusses the factors associated with an increased risk of left ventricular free wall rupture, such as large infarct sizes, gender, advanced age, and interval time between symptom onset and angiography. The overall goal is to contribute to the understanding and management of this life-threatening condition, ultimately improving patient outcomes and reducing mortality rates associated with acute myocardial infarction complications.[2,3]

CASE REPORT

A 69-year-old man with dyspnea and chest symptoms was referred to our department. He had diaphoresis and substernal severe chest pain a month ago. He was treated at the closest hospital, where a stent was implanted in the ostial-distal Left Circumflex (LCx) artery, primary PCI was performed and posterior STEMI was discovered. Three weeks later, he experienced dyspnea and chest pain. Physical examination revealed pansystolic murmur grade III/VI at apex then re-angiography revealed LV aneurysm and stent thrombosis in the LCx artery. Massive pericardial effusion with free wall rupture was seen on the echo. He was later sent to our hospital for additional care. He was breathing heavily while in our emergency room. His blood pressure was 125/74 (94) Heart rate was 94 bpm, Respiratory rate 24 times/minute, SpO2 was 98%, there were no rales, and his ankles had pitting edema. Bedside Echo, revealed a Left Ventricle (LV) aneurysm and a large, localized pericardial effusion without tamponade, LV aneurysm with possible rupture of the free wall. Following his admission to the intensive care unit, he had heart surgery. The patient's vital signs include a weak overall appearance, blood pressure of 125/74 (94) mmHg, heart rate of 95 bpm, Respiratory rate of 24 x/minute, SpO2 100% with 3 lpm nasal, and conjunctiva anemia observed on physical examination. There were grade 4/6 pansystolic murmur in the apex of the heart, and rales one-third of the lung's bottom. Medical findings from the Angiography indicate coronary artery disease (CAD) with one-vessel involvement (CAD1VD), a total in-stent thrombosis at the proximal LCx, and failed wiring in the LCx. An LV graph also reveals an LV aneurysm, but no contrast extravasation from the LV.

From echocardiography, the LVH (Left Ventricle Hypertrophy) is concentric, with a visualization of an LV aneurysm in the posterior LV. Pericardial effusion has a size of 50 mm with a visualization of fibrin. Free wall rupture has a size of 30 mm. The systolic function of the LV has decreased, with an Ejection Fraction (EF) of 37% by Sympson and 32% by Teichz. Diastolic function of the LV is mildly impaired, with a grade I dysfunction (E/A 0.7). Systolic function of the Right Ventricle (RV) has also decreased, with a Tricuspid Annular Plane Systolic Excursion (TAPSE) of 7 mm. There is mild mitral regurgitation (MR), and there is an 18% variation in mitral

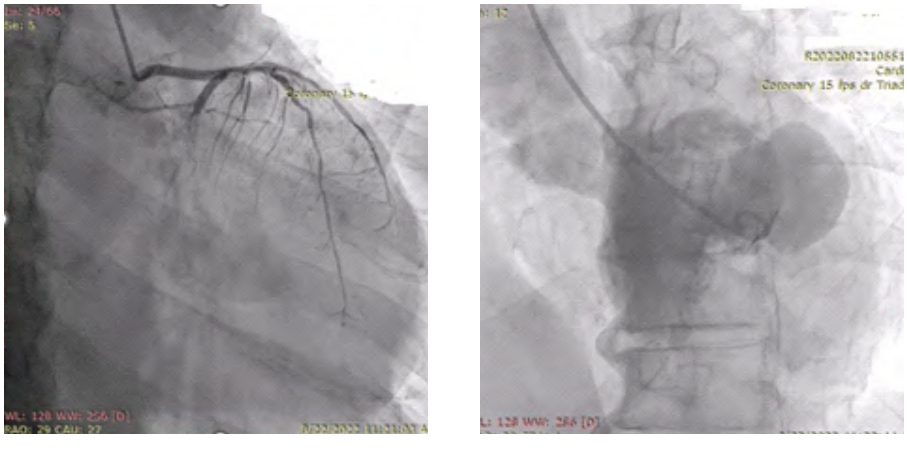

Figure 1. Angiography showed a total instent thrombosis at the proximal LCx, and failed wiring in the LCx. An LV graph also reveals an LV aneurysm, but no contrast extravasation from the LV.

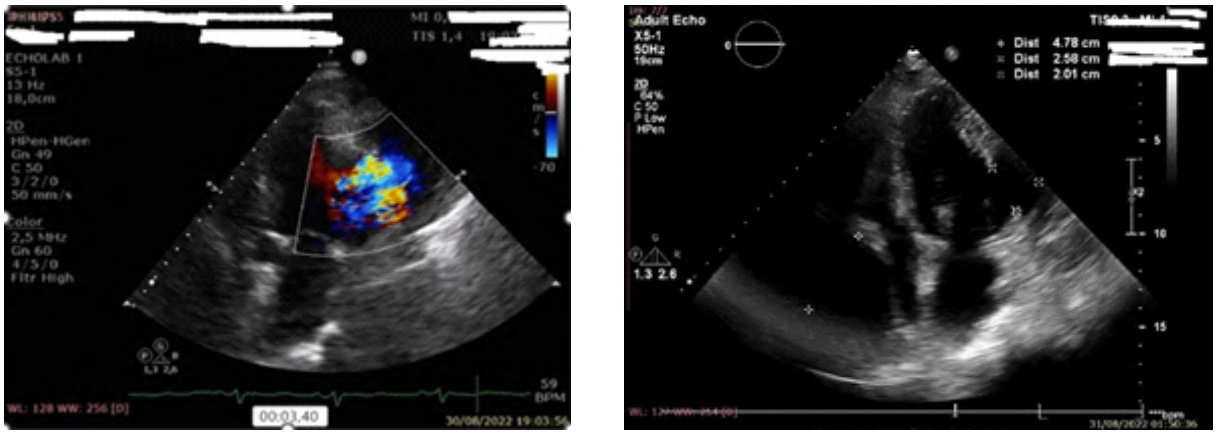

Figure 2. Echocardiography of Pseudoaneurysm (left) and Massive Pericardial Effusion (right)

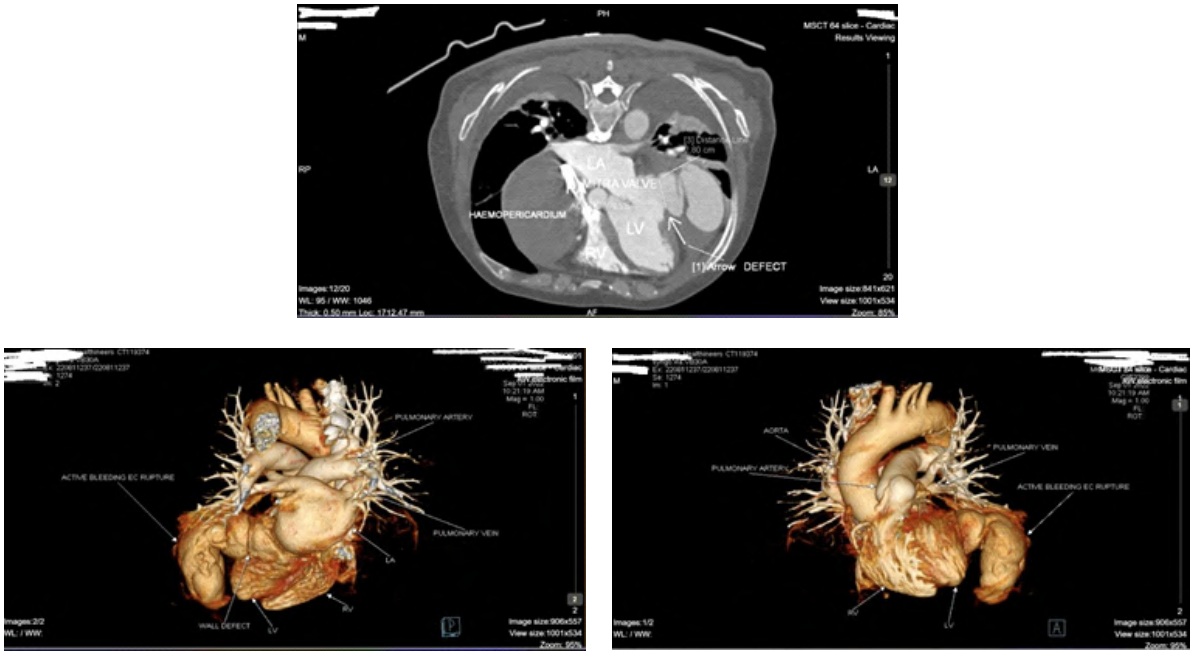

Figure 3. MSCT Cardiac of LV Pseudoaneurysm and Massive Pericardial Effusion

inflow. From Multi slice Computerized Tomography (MSCT) Cardiac the patient has an extravasation of contrast through a defect on the lateral ventricle of the left heart, with a diameter of approximately 2.8 cm and a distance of approximately 1.7 cm from the mitral valve. This has resulted in hemopericardium, which is accompanied by active bleeding, suggesting a possible free wall rupture of the left ventricle. Right atrium appears to have decreased in size, with a long axis of approximately 4.92 cm and a short axis of approximately 1.66 cm.

During the surgery, a clot was found behind the right atrium, and a massive pericardial effusion was present in the pseudoaneurysm of the left ventricle, amounting to approximately 150 ml. A closure was performed on the free wall rupture using gortex, and a delayed sternal closure was carried out. Then, he performed sternal closure 3 days after surgery. During monitoring in cardiac intensive care, he was well recovered. Evaluation by transthoracic echocardiography and chest X-ray there was no expansion of pericardial effusion, no shunt of LV free wall, and improved LV function. The substernal drain itself showed improving significantly from 300 to 5 ml, on the nine days. later he showed improving in all parameters. The patient was stepdown to the cardiac ward.

DISCUSSION

Left ventricular free wall rupture and LV aneurysm formation are serious, yet rare, structural complications

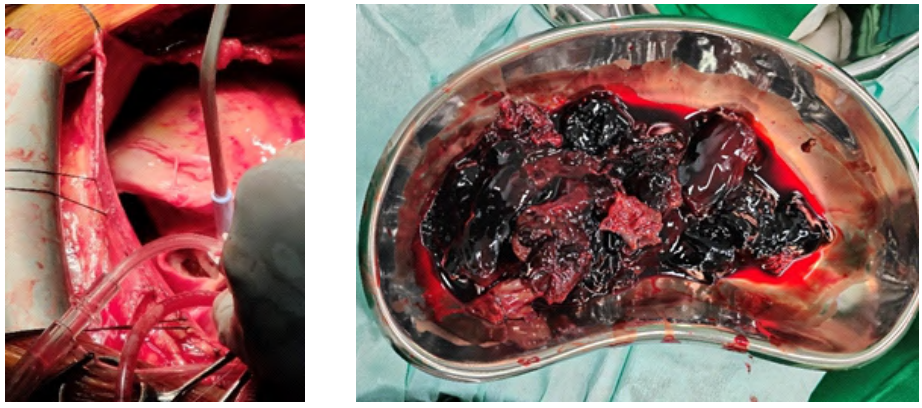

Figure 4. Result of Repair LV Free Wall Rupture + Pericardial Effusion Evacuation

post-myocardial infarction. Patients was referred from a previous hospital with an LV aneurysm found during coronary artery angiography (CAG). Physical examination and echocardiography were performed. Patient was diagnosed with LV free wall rupture differential diagnosis with LV pseudoaneurysm and aneurysm, massive pericardial effusion without cardiac tamponade signs, and previous angiography indicated total in-stent thrombosis in LCx. He was completely in a state of failure due to LV free wall rupture and massive pericardial effusion. A continued dose of furosemide and optimization of dual antiplatelet (aspirin and clopidogrel were chosen), ace-inhibitor, and mineralocorticoid receptor antagonist were administered. In this case, the process of left ventricular pseudoaneurysm caused by rupture of the left ventricular wall after myocardial infarction was clear. Then, patient was planned for urgent repair of LV free wall rupture and evacuation of pericardium effusion, and Coronary Artery Bypass Graft (CABG) as needed to improve prognosis as most of patients with pseudoaneurysms treated conservatively have poor prognosis in one series and the mortality rate at the first 2 year is almost 50%. This case report showed us the complex complications after in-stent thrombosis after acute myocardial infarction that should we avoid.[3–5]

Pseudoaneurysms in the left ventricle are typically located on its lateral or diaphragmatic surface. LV pseudoaneurysms are prone to rupture and have a tendency to expand quickly. Once the diagnosis is established, prompt surgery is required. Further testing, like as Magnetic Resonance Imaging (MRI) or MSCT cardiac, may be necessary to confirm the diagnosis of LV pseudoaneurysms, as supplementary exams like echocardiography may not be sufficient.[8]

There are two main categories into which Free Wall Rupture falls, Oozing type: this kind of bleeding is marked by sluggish, unclear bleeding that builds up in the pericardial sac.[9] Blow-out type: characterized by a large hemorrhage and a macroscopic defect that causes abrupt tamponade.[9]

The patient's initial symptoms might range from minor chest discomfort to severe chest pain or even abrupt death, depending on the patient's clinical status. The coronary arteries that are most frequently involved are LAD and LCX. Heart failure owing to AMI is a particular symptom of free wall rupture, even though the clinical signs of the rupture are less specific for cardiac tamponade than for the rupture itself. Timely referral for surgery is essential. When tamponade and hemodynamic instability are proven, pericardiocentesis can save lives, However, blood clots could be discovered in the pericardial sac.[9]

The principles of surgical treatment of LVFWR are to relieve tamponade, close the tear and/or stop the bleeding, anchor the repair on healthy tissue, and minimize distortion of heart geometry while preventing the recurrence of rupture or pseudoaneurysm formation. The chosen method for surgical repair is usually dictated by the type of rupture, its surrounding tissues, and the presence of concomitant lesions. Some authors believe that coronary angiography should be promptly performed as soon as pericardial effusion is noted in AMI patients before they deteriorate. The knowledge of coronary status is of great help in deciding where and how to place the sutures during surgery; in addition, proper revascularization of the diseased vessels supplying the non-infarcted area at the time of LVFWR repair (concomitant coronary artery bypass grafting) has been shown to exert a positive impact on survival and freedom from angina.[6,7]

One serious risk related to stent implantation is stent thrombosis. Myocardial infarction, cardiogenic shock, hematoma, pseudoaneurysm, retroperitoneal hemorrhage, arrhythmia, thrombus development, and stroke are among the outcomes that might occur from undetected or untreated problems. Following AMI, the patient's clinical and hemodynamic status remained stable, while mechanical problems such as LV pseudoaneurysm and free wall rupture were noted. Subacute stent thrombosis, which happened between

24 hours and a month following stent implantation, was identified as the root cause of these problems. Hemopericardium behind the Right Atrium caused a huge pericardial effusion with imminent tamponade, which avoided tamponade symptoms and did not require inotropic support. Following comprehensive evaluations to determine the best surgical strategy, the pericardial effusion was surgically evacuated during the intervention and healing of the free wall rupture following the patient's cessation of antiplatelet medication.[10–12]

CONCLUSION

AMI may result in problems related to embolism, arrhythmia, mechanical, ischemia, or inflammation. Significant clinical improvement after the emergence of surgical mechanical problems following acute myocardial infarction. As seen in our case, free wall rupture can develop into a Pseudoaneurysm, if it happened then precise care about free wall rupture can be saved.

CONFLICT OF INTEREST

The author has no conflicts of interest that could affect the results or interpretation in this report.

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Case Report

Sleeve Gastrectomy and Liver Cyst Unroofing in Morbid Obesity with Multiple Liver Cysts: A Case Report

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Abstract

Background : Obesity has become a major global health issue which leads to various complications, including hepatic diseases. However, we found a rare case of morbid obesity and symptomatic multiple liver cysts. This article aims to represent a rare case of morbid obesity and multiple liver cysts surgically managed by sleeve gastrectomy and liver cyst unroofing which were performed in a single surgery.
Case report : 41-year-old female presented with morbid obesity and blunt intermittent abdominal pain in the right upper quadrant. Stage II hypertension, tenderness on the right upper quadrant of the abdomen and epigastrium were found in clinical assessment. Lipid profiles were shown to be elevated. Abdominal CT revealed fatty liver and multiple cystic lesions in all hepatic segments.
Discussion : Non-parasitic liver cysts affect 2–18% of the global population, with a higher prevalence in females possibly due to hormonal factors. Obesity is associated with hormonal alterations, potentially leading to increased secretion of FSH and LH.
Conclusion : Sleeve gastrectomy and liver cyst unroofing may be considered as a treatment strategy for patients with morbid obesity and multiple liver cysts.

Keywords : obesity, sleeve gastrectomy, liver cyst

INTRODUCTION

Obesity has emerged as a significant global health issue in recent years. The worldwide number of overweight and obesity people have increased from 105 million in 1975 to 641 million in 2014, resulting in more than one-third of the world's population now being categorized as overweight or obese.[1] A study conducted by Kelly *et al*. stated that 57.8% of the global population will be overweight or obese by 2030 if the current trends persist.[2] Obesity is characterized by a body mass index (BMI) of over 30.0 kg/m^2. Meanwhile, morbid obesity is defined as a BMI of 40.0 kg/m^2 or higher, while also experiencing obesity-related health conditions.[3]

Obesity is associated with various complications, including hepatic diseases.[3] Up to 90% of patients in a cohort who experienced bariatric surgery have non-alcoholic fatty liver disease (NAFLD).[4] However, we found a rare case of morbid obesity presented with multiple liver cysts. Liver cysts are characterized as small abnormal fluid-filled sacs that are formed in the liver tissue.[5,6] The prevalence of liver cysts in the United States ranges 15–18%.[7] These cysts are often asymptomatic and typically identified incidentally on imaging studies. The exact cause of most liver cysts is not fully understood, and their etiologic pathogenesis remains unclear.[8]

This article aims to represent an approach where two procedures, sleeve gastrectomy and liver cyst unroofing were performed in a single surgery. We believe our successful treatment approach may provide valuable insights and guidance for surgeons who encounter similar cases in their clinical practice.

CASE REPORT

A 41-year-old woman came to our outpatient clinic with a chief complaint of blunt intermittent abdominal pain in the right upper quadrant for 2 years. The patient had morbid obesity (body weight: 134 kg, body height 163 cm, BMI: 50.4 kg/m^2) with 13 years of weight gain. She denied having fever, jaundice, nausea, and vomiting. She had no history of alcohol consumption. There was no significant family history of malignancy.

Upon clinical assessment, stage II hypertension with blood pressure of 190/110 mmHg and tenderness on the right upper quadrant of the abdomen and epigastrium were identified. There was no sign of hepatomegaly, cirrhosis, or liver nodule. Other clinical findings were insignificant.

The hematological and liver function tests were within normal range. Elevated lipid profiles were identified (total cholesterol: 207 mg/dL, LDL: 164 mg/dL, and TGL 162 mg/dL). Immunological studies for hepatitis B and C were negative. An abdominal CT was performed, revealing fatty liver and multiple cystic lesions in all hepatic segments (largest diameter in segment IV; anteroposterior 5.7 cm x latero-lateral 7.3 cm x craniocaudal 6.4 cm).

Laparoscopic sleeve gastrectomy and liver cyst unroofing were performed under general anesthesia. The patient was positioned reverse trendelenburg with abducted legs. An infraumbilical incision was made for insertion of an 11 mm optical view trocar into the abdominal cavity. Then, the abdominal cavity was insufflated with CO2 gas. The second trocar (12 mm) and third trocar (5 mm) as the working trocars, the fourth trocar (5 mm) as the assistant trocar, and the fifth trocar as the liver retractor were inserted into the abdominal cavity. The positions of the trocars are shown in Figure 2a. Hepatic cysts on the left lobe with diameter more than 2 cm were unroofed, as shown in Figure 2b. Smaller hepatic cysts (d < 2 cm) were drilled. Then, sleeve gastrectomy was performed by dissecting greater curvature of the stomach at 5 cm from the pyloric sphincter to 1.5 cm from the gastroesophageal junction using linear staplers, as shown in Figure 2c. Then, the stomach was tested with 75 mL of methylene blue to ensure no leakage was present. Omentoplasty was also

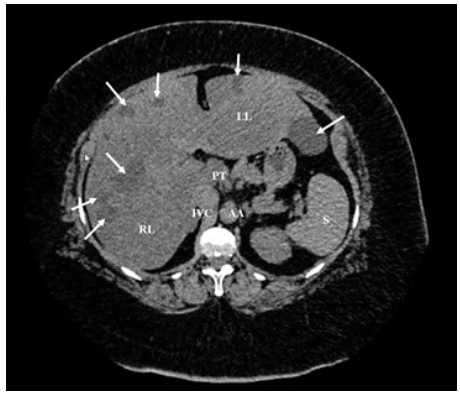

Figure 1. Abdominal CT scan showed multiple liver cysts (arrows) in the right lobe (RL) and left lobe (LL) of the liver. Other structures can be identified in relation to the liver: portal triad (PT), inferior vena cava (IVC), abdominal aorta (AA), and spleen (S).

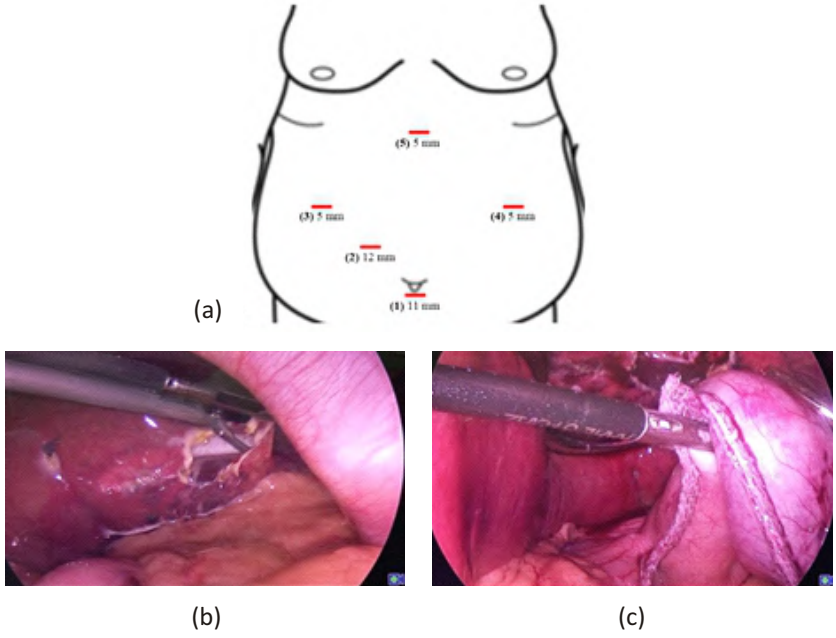

Figure 2. (a) The location of skin incisions with size of the ports; (b) liver cyst unroofing; (c) sleeve gastrectomy.

performed on the gastric line resection. Lastly, a drainage tube was set and incisions were closed.

The postoperative condition was uneventful. Drainage production was monitored every day, and it was found to be less than 50 mL on day 2 post-procedure. The patient was discharged on day 5 in good conditions. Home visit was done after 6 months, and she has lost 23 kg with no complaint of right upper quadrant abdominal pain.

DISCUSSION

The prevalence of non-parasitic liver cysts is 2–18% among global population, with significantly higher likelihood of occurrence in females.[9] This may due to higher levels of FSH and LH in premenopausal women.[10] In addition, obesity is associated with alteration of hormonal pathways in women. Estradiol levels were found to be lower in premenopausal obese women, the mechanisms for this association are not clearly identified.[11] Lower estradiol levels in obesity may lead to negative feedback to hypothalamus-pituitary axis, thus higher FSH and LH levels are secreted.[12] It is important to note that not all patients with morbid obesity will develop liver cysts, and the impact of obesity may vary from one person to another. Therefore, further research may be necessary to explore the possible correlation between liver cysts and obesity.

The symptoms of non-parasitic liver cysts are related to the distention of Glisson's capsule as the cyst enlarges or experiences intracystic hemorrhage. Unusual cases of infected cysts may also be symptomatic.[13] Surgical intervention is indicated only for patients demonstrating noticeable symptoms.[13,14] Symptomatic liver cysts may be managed by several surgical methods, such as percutaneous aspiration and sclerotherapy, open or laparoscopic unroofing, radical cystectomy or liver resection.[15] Simple cyst aspiration is not preferred due to high recurrence rates, up to 100% of cases.[16] Injection of sclerosing agent following aspiration can decrease recurrence rates to less than 1%.[17] However, this method cannot be applied if there is a communication between the cyst with the biliary tree.[15] In addition, larger cysts with diameters exceeding 15 cm appear to have 50% chance of recurrence.[18] Liver cyst unroofing can be conducted by open or laparoscopic procedure by removing a part of, or the entire cyst wall with fulguration of the cyst bed. The suitability for laparoscopic unroofing is influenced by its location within the liver and the operator's skill level.[15] This technique seems to have low recurrence rates between 0% and 13.8%.[19] Recurrence of treated cysts can be caused by several factors such as inadequate unroofing, performing the procedure on recurrent cysts with potential adhesion formation, and cysts that are deep-seated or situated in the liver's posterior segments.[15]

The 2015 American Diabetes Association guideline recommended that bariatric surgery should be considered in patients with severe obesity (BMI ≥35 kg/m^2) and obesity-related complications including type 2 diabetes mellitus which are challenging to control with lifestyle modification and pharmacological therapy.[20] The two main surgical procedures regarded as the standard of care for weight-loss surgery are laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG).[21] LRYGB is still considered the gold standard for weight-loss susrgery.

This procedure involves two main steps: creating a small gastric pouch by separating the cardia from the rest of the stomach, and dividing the small intestine 30–50 cm below the ligament of Treitz. The distal end of the divided intestine, known as the Roux limb, is brought up in an antecolic fashion and connected to the new gastric pouch. This complex surgery involves rerouting the intestines, which may lead to long-term vitamin and mineral deficiencies, longer hospital stay, and has a higher rate of perioperative complications. Meanwhile, LSG only involves removing approximately 80% of the lateral aspect of the stomach vertically, leaving a long, tubular gastric sleeve. This procedure induces rapid and substantial weight loss comparable to that of LRYGB and does not cause vitamin and mineral deficiencies.[22]

Our case may suggest a possible guide for surgeons who are sought to surgically treat patients with morbid obesity and multiple liver cysts. However, a comprehensive long-term follow-up is essential to evaluate whether the procedure contributes to the improvement of radiologic and laboratory outcomes.

CONCLUSION

Sleeve gastrectomy and liver cyst unroofing may provide a possible treatment strategy for patients presented with morbid obesity and multiple liver cysts. Further research is needed to compare pre- and post-operative liver imaging and laboratory results and analyze the relationship between liver cyst and obesity.

Patient consent for publication
Patient/guardian consent obtained.

Disclosure
The authors declare that they have no conflict of interest.

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Case Report

Acute Inferior ST-elevation Myocardial Infarction Arising from Wrap-Around Left Anterior Descending Artery Occlusion

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Abstract

Background : Acute myocardial infarction (AMI) remains a leading cause to global morbidity and mortality. Inferior MI predominantly stems from the right coronary artery (RCA) in more than 80% of instances, the left circumflex coronary artery (LCx) in fewer than 20% of cases, and infrequently from the left anterior descending artery (LAD). This case report aims to highlight a rare occurrence of LAD occlusion initially manifested as inferior MI.
Case : A 56-year-old male presented with typical chest pain lasting for 6 hours. Vital signs were within normal range. Initial electrocardiogram (ECG) revealed ST-segment elevation in inferior leads (II, III, aVF). Laboratory tests indicated elevated troponin levels (>25ng/mL). Coronary angiography identified the culprit lesion as the LAD, which wrapped around the apex.
Discussion: While ECG alterations are valuable in identifying thrombosed vessels during AMI, the presence of simultaneous ST elevation in both inferior and anterior leads can hinder clinicians' ability to determine the specific artery affected by the infarction. Our case, depicting a scenario where both the right and left coronary arteries are co-dominant, showed complete occlusion at the mid-distal wrap-around LAD, resulting in ST-elevation observed in both inferior and anterior leads.
Conclusion : The existence of inferior ST-segment elevation alongside alterations in anterior leads could imply occlusion of the wrapped LAD.

Keywords : Inferior ST elevation; total occlusion, acute myocardial infarction; wrap around LAD

INTRODUCTION

Acute ST-segment elevation myocardial infarction (STEMI) stands as a predominant cause of global morbidity and mortality. This condition arises when coronary artery blockage triggers transmural myocardial ischemia, leading to myocardial necrosis or injury. The interplay of inflammation and instability of coronary atherosclerotic plaque contributes to thrombus formation, a hallmark of acute MI.[1]

Inferior STEMI represents approximately 40 to 50% of all STEMI occurrences, boasting a relatively low mortality rate below 10%. However, the presence of complicating factors such as cardiogenic shock, cardiac arrhythmia, heart block, and right ventricular infarction can heighten morbidity and mortality. Inferior MI predominantly stems from the right coronary artery (RCA) in more than 80% of instances, the left circumflex coronary artery (LCx) in fewer than 20% of cases, and infrequently from the left anterior descending artery (LAD).[2,3] We present a rare occurrence of LAD occlusion initially manifested as inferior MI.

CASE REPORT

A 56-year-old male was referred to our hospital with retrosternal chest pain radiating to both shoulders, accompanied by nausea and diaphoresis six hours before admission. He was an active smoker with a ten-year history of diabetes mellitus. Upon physical examination, his pulse was 68 beats/min, blood pressure 130/80 mmHg, and oxygen saturation 96% on room air. There were no signs of tachypnea, cardiac murmurs, abnormal breath sounds, or peripheral edema.

Initial electrocardiography (ECG) conducted one hour after symptom onset at the district hospital revealed ST-segment elevation in the inferior leads (II, III, aVF) and occasional premature ventricular complexes (PVCs). Subsequent ECG six hours post-onset depicted ST-segment elevation in both inferior and anterior leads (V2-V4) without evolution in inferior leads. Follow-up ECG at six hours post-onset revealed slight ST elevation in precordial leads (Figure 1).

Laboratory investigations demonstrated a high troponin level (>25 ng/mL), while complete blood count and metabolic panel tests were within normal range. Chest X-ray findings were unremarkable. Initial management in the emergency room comprised antiplatelet therapy and intravenous heparin before transfer to the catheterization laboratory, with a door-to-wire time of within 45 minutes.

Coronary angiogram revealed a normal left main artery, total occlusion (thrombus type) at the mid-distal LAD, proximal narrowing of 60–70% in the LCx artery, and 70% distal stenosis in the RCA (Figure 2). Primary percutaneous coronary intervention (PPCI) of the mid-distal LAD was performed using two drug-eluting stents, ensuring perfusion to the myocardial wall (Figure 3).

Follow-up ECG demonstrated Q-wave evolution and ST-T changes in anterior leads (V2-V4) without evolution in the inferior leads, consistent with LAD as the culprit lesion.

The patient received aspirin, ticagrelor, statins, beta-blockers, and ACE inhibitors. He remained in the coronary care unit for two days before discharge in good general condition, with scheduled outpatient follow-ups.

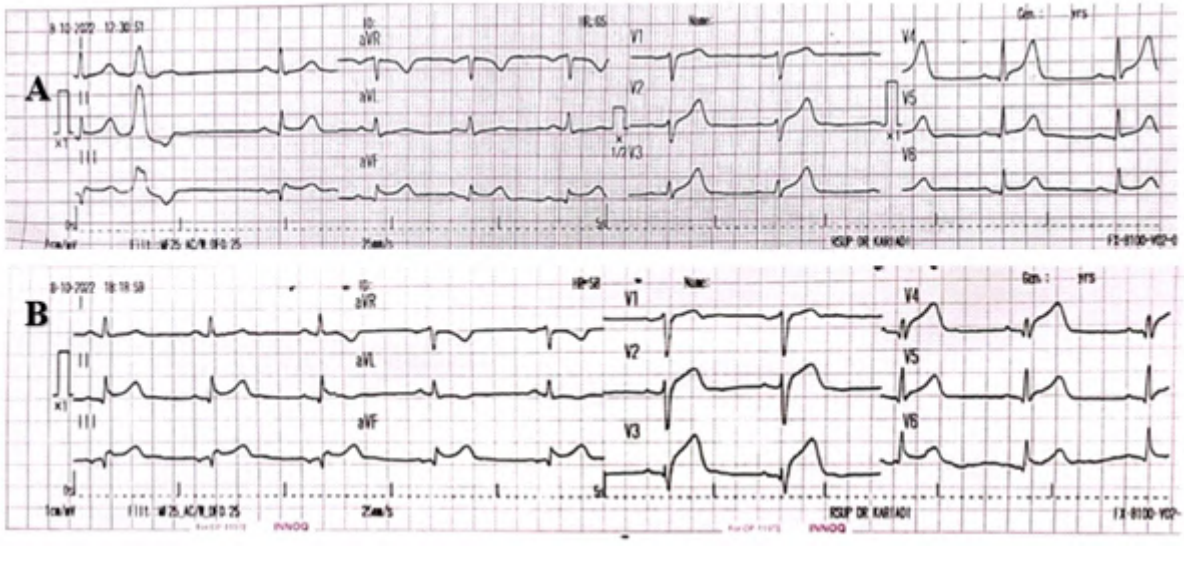

Figure 1. ECG at one hour onset showed ST-elevation in the inferior lead with occasional PVCs(A). Subsequent follow-up ECG at 6 hours after onset revealed ST elevation in the precordial leads (B).

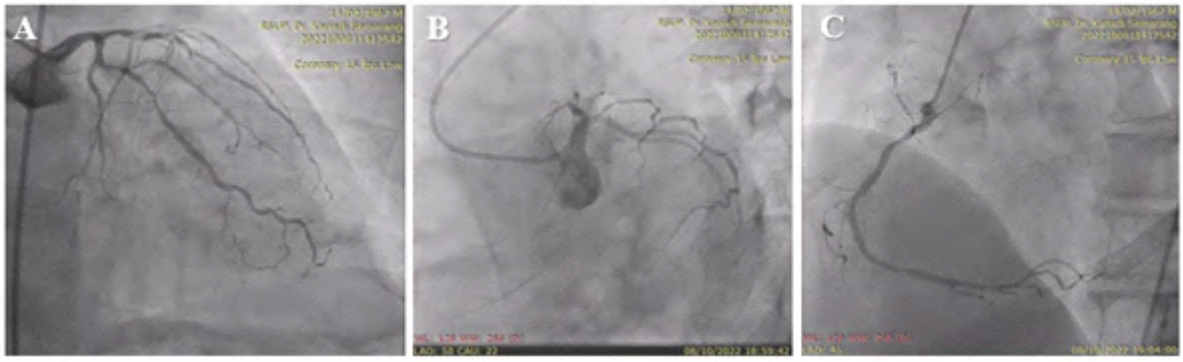

Figure 2. Coronary angiogram, showing a 60–70% stenosis at the proximal LCx (A), total occlusion at the mid-distal LAD (B), and a 70% stenosis at the distal RCA (C).

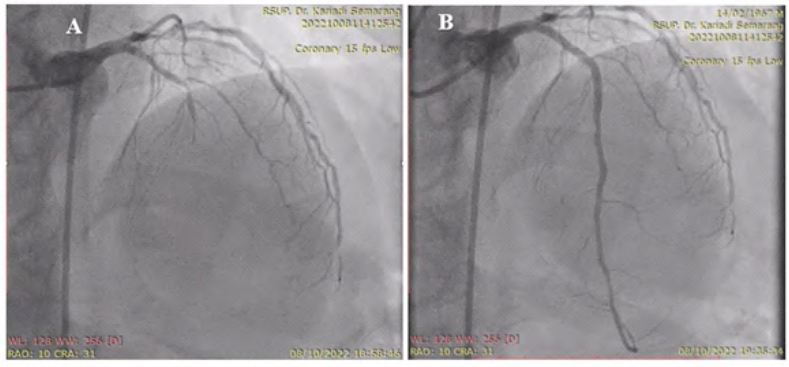

Figure 3. Total occlusion observed at the mid-distal LAD (A). Subsequent to PPCI intervention, a wrap-around LAD configuration was evident (B).

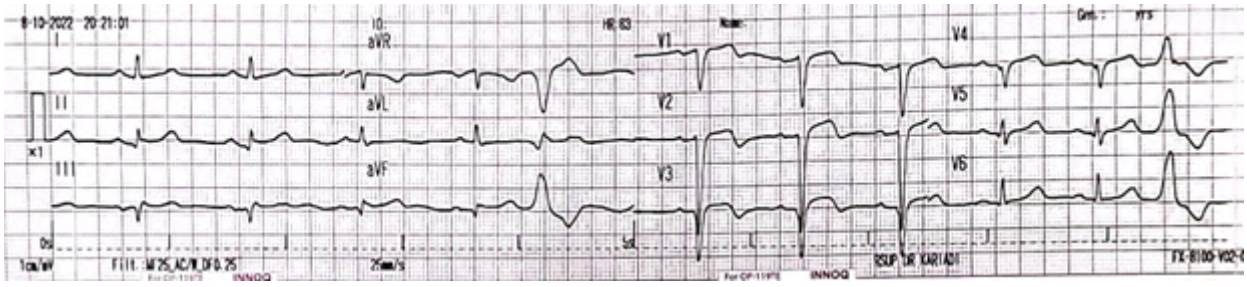

Figure 4. 12-lead ECG showed evolution in the precordial leads instead of the inferior lead after PPCI.

DISCUSSION

Twelve-lead ECG is pivotal in diagnosing patients experiencing acute myocardial infarction (AMI). In STEMI cases featuring ST-segment elevation in inferior leads (II, III, and aVF), analyzing ST elevation and depression across multiple leads aids in identifying the thrombosed artery (RCA or LCx) and even pinpointing the occlusion site. However, simultaneous presentation of ST elevation in both inferior and anterior leads on ECG can pose challenges in evaluating the true infarct-related artery.[4–7]

This scenario occurred in our patient, who presented with AMI displaying ST-segment elevation in both inferior and anterior leads concurrently. CAG revealed total occlusion solely in the LAD, which wrapped around the apex to supply both inferior and anterior myocardiuma phenomenon known as a "wrap-around LAD".[8]

In cases of wrap-around LAD, anterior leads ST segment elevation is observed while remains iso-electric in the inferior leads if the occlusion is proximal to the diagonal branch (D1). However, if the occlusion is distal to D1, ST segment elevation may occur in both

anterior and inferior leads concurrently. Inferior only ST segment elevation on ECG, particularly in patients with dominant left coronary circulation, can be found when there's very distal LAD occlusion.[9]

Our case, illustrating a co-dominant right and left coronary artery with total occlusion at the mid-distal wrap-around LAD, underscores the potential for more extensive myocardial damage compared to non-wrap-around LAD occlusion. Consequently, immediate reperfusion is critical, and meticulous medication management and follow-up care are imperative, even post-discharge, to address potential heart failure complications.[10,11]

CONCLUSION

The role of ECG for identification of the culprit occlusion site in inferior STEMI is crucial. It plays a vital role in determining the location of the culprit lesion in most instances, aiding appropriate lesion management.

Inferior ST-segment elevation in association along with changes in anterior lead may suggest wrapped LAD occlusion. Clinicians should carefully assess the underlying cause and swiftly treat the affected vessel.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research manuscript should adhere guidelines as follow:

Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, method, result, 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 (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
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 :
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CASE REPORT

Title :
1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

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2. Consists of maximum 250 words
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4. Is presented in English

Introduction :
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2. Is supported by relevant and strong references

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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.
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2. Suggestion consists of improvement for case management.

Reference :
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