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Management and quality of life extranodal non hodgkin lymphoma of testis
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FOREWORD

Alhamdulillah, praised to Allah, Journal *Qanun Medika: Fakultas Kedokteran Universitas Muhammadiyah Surabaya* vol 06 no 01 has been published. It consists of 15 articles including 1 literature review, 3 case report and 11 research articles in the medical field. In addition, there is 1 international article from India. We would like to thanks our reviewers and editorial board members who helped us in this publication. In order to be internationalized, we only published articles written in English since July 2019. We hope that these articles can be read widely both by domestic and foreign readers.

Thank you,

Yelvi Levani, MD.,M.Sc

Editor in Chief

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Literature review

Mental and behavioral disorders due to substances during the COVID-19 Pandemic: Prevalence, diagnosis, and management

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ABSTRACT

COVID-19 (Coronavirus Disease 2019) is still a significant problem; therefore, mental health issues and COVID-19 are starting to get attention because of the increasing psychological impact and mainly because of Substance Use Disorder (SUD). Further study is required on this issue. This paper aimed to determine the prevalence, diagnosis, and treatment of SUD during the COVID-19 pandemic. This literature review is gained from scientific articles with a range of publication years from 2016 to 2021 about SUD During the COVID-19 pandemic based on Prevalence, Diagnosis, and psychotherapy of the published journal using Pubmed, Google Scholar, and SAGE Journals, and then critically reviewed. The prevalence of SUD patients during the COVID-19 pandemic has increased; however, digital psychotherapy strategies for SUD patients have been found and proved effective during the pandemic. In conclusion, the COVID-19 pandemic impacts a person's mental and behavior and could be a high-risk opportunity for substance abuse. Therefore health workers must improve health services for SUD patients to receive the health access needed even in a pandemic.

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INTRODUCTION

The COVID-19 Pandemic had a significant impact on lives around the world. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. To reduce the spread of the virus and help health workers to contain it, the government began imposing a "quarantine" starting in March. Efforts have been made, among others, by urging the public to stay at home, limiting physical distance, and closing public facilities such as schools, restaurants, and entertainment venues (Cucinotta & Vanelli, 2020). Since the policy came into effect, mental health and COVID-19 issues have begun to receive attention due to increasing concerns about the psychological and mental health impacts. Several studies have found an increasing prevalence of various psychological disorders such as anxiety, depression, stress, and insomnia (Dietze et al., 2020; Wang et al., 2020; Zhou et al., 2020). To Overcome these psychological problems, people tend to engage in addictive behaviors such as substance use and other addictive behaviors (Dietze et al., 2020; Elhai, Yang, Mckay, & Asmundson, 2020; Spitzer, Kroenke, Williams, & Löwe, 2006)

According to data CDC's National Center for Health Statistics shows approximately 93,331 drug overdose deaths in the United States in 2020, an increase of 29.4% from the predicted 72,151 deaths in 2019 (Cucinotta & Vanelli, 2020). As of June 2020, 40.9% of 5,412 United States adults experienced adverse mental health or behavioral symptoms, including anxiety or depression disorders (30.9%), trauma and stress-related disorders associated with COVID-19 (26.3%), initiating or increasing substance use (e.g., alcohol, legal or illegal drugs, or prescription drugs taken in a manner not recommended by a doctor) to manage stress or emotions related to COVID -19 (13.3%), and seriously considered suicide (10.7%). The prevalence of anxiety symptoms and depressive disorders was 3 and 4 times higher, respectively than those experienced during the second quarter of 2019 (anxiety disorders = 25.5% versus 8.1%; depressive disorders = 24.3% versus 6.5%), and Ideation suicides more than doubled in 2018 (10,7% versus 4,3%) (Dietze et al., 2020).

According to research by Marel et al. in 2021, a cohort study showed that patients with mental disorders who use Substance Use Disorder (SUD) increase the risk (80%) and complications of Covid-19. In addition, the consequences of Covid-19, especially physical distancing, increase the risk for patients with mental disorders to harm themselves with drugs and substances. Loneliness, independent isolation, financial problems, and stress of economic factors can also make a person experience mental disorders (such as depression, anxiety, self-harm, and suicidal ideation). Therefore this makes the prevalence of SUD (Substance Use Disorder) high (Marel, Mills, & Teesson, 2021). The COVID-19 pandemic has made people with substance abuse disorders reluctant to come for consultations to health facilities which has led to a decrease in treatment compliance so that the latest anticipation and management are needed for people with mental health and substance abuse (López-Pelayo et al., 2020)

Based on that phenomenon, there are differences in mental conditions and behavior in people who abuse substances before and during the COVID-19 pandemic. Therefore, the authors are interested in collecting information on the prevalence, diagnosis, and management of substance-induced mental and behavioral disorders in the COVID-19 pandemic so that patterns of substance use and treatment challenges can be identified in the COVID-19 pandemic. Mental and behavioral disorders due to substances during the COVID-19 pandemic. Narrative Literature Review by title "Mental and Behavioral Disorders Due to Substances

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(SUD) During the COVID-19 Pandemic: Prevalence, Diagnosis, and Management" is expected to be a reference and reading material for further research.

METHOD

The making of this Literature Review is done by seeking information from sources following the formulation of the problem from search engines such as Pubmed, Google Scholar, and SAGE Journals with the year of publication from 2016 to 2021. The keywords used in this Literature Review are ((((Mental and Behavioral Disorders)) AND substance use during the COVID-19 Pandemic) AND substance use before the COVID-19 Pandemic) AND (prevalence, diagnosis, and management). The selected articles and journals according to inclusion and exclusion criteria to make a Literature Review. Twenty relevant articles were managed using the Mendeley reference manager application, then tabulated and discussed through the information.

RESULTS

In making this literature review, we searched some information based on our keywords with a literature search engine such as PubMed, Google Scholar, and *Sage Journal*. Our keywords *((((Mental and Behavioral Disorders)) AND substance use during the COVID-19 Pandemic) AND substance use before the COVID-19 Pandemic) AND (prevalence, diagnosis, and management)*, overall had found 26,791 articles. Then we did screen the articles to 5 years time span and selected some types of articles, including *research articles, literature reviews, clinical research & reviews* (n=196). Not all of the journals we found could be accessed (accessed journals n=32). Then we selected some articles that matched our inclusion which is related to substance-induced mental and behavioral disorders during the COVID-19 pandemic based on prevalence, diagnosis, and management in English. Final articles that meet the inclusion criteria (n=20) was chosen from *Pubmed* (n=18), *Google scholar* (n=1), *Sage Journal* (n=1) and *managed* with *Mendeley Reference Manager*. Quantitative and Qualitative data was extracted manually to Microsoft Word, selecting important points based on our PICO.

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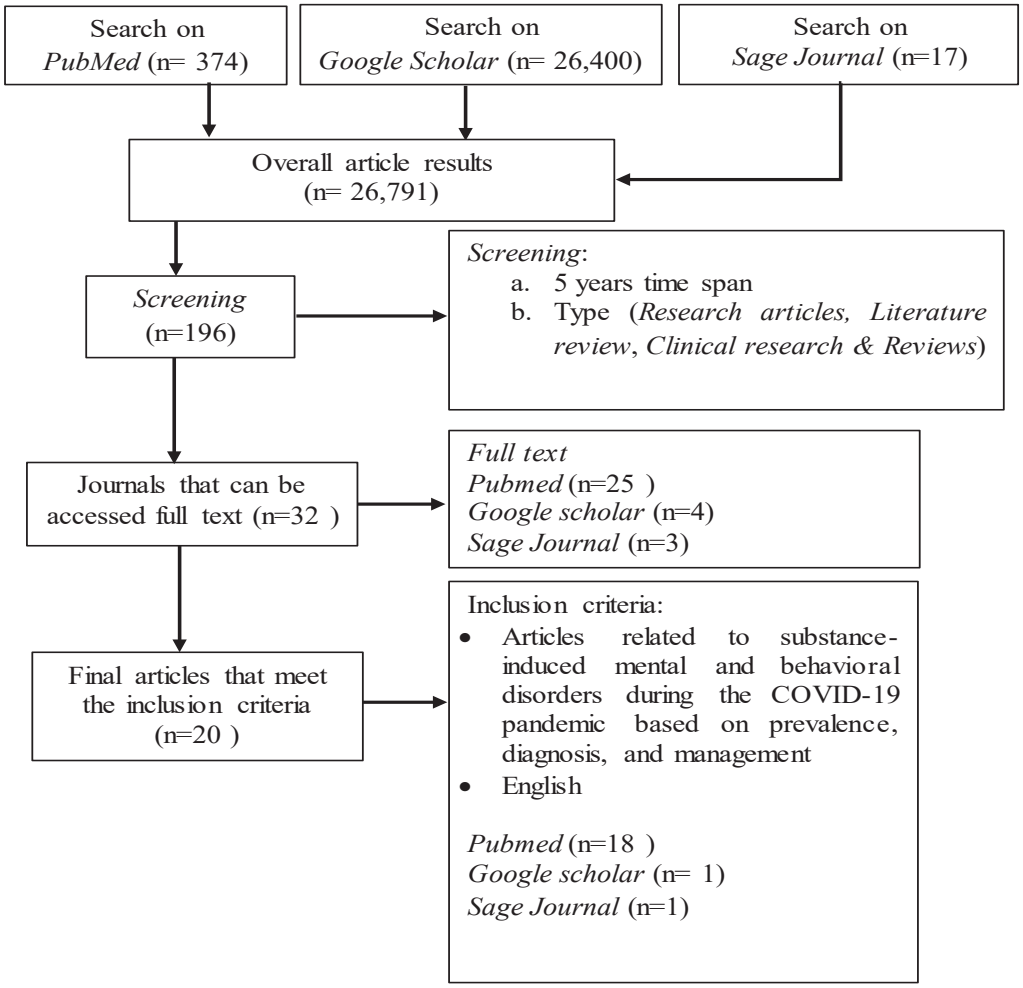

Figure 1. Workflow of literature searching

DISCUSSION

Mental and behavioral disorders due to substance use are health problems that need attention in the era of the COVID-19 pandemic. Abuse of alcohol and drugs can worsen the quality of health, education system, and social life that can bring dangers such as cases of alcohol-related car accidents, drug-related violence, and drug overdose. In this case, the substance is defined as a psychoactive compound that has the potential to cause health and social problems, including addiction, for example, substances that may be legal such as alcohol and tobacco; illegal (heroin and cocaine); or medications prescribed for medical purposes such as hydrocodone or oxycodone (for example, Oxycontin, Vicodin, and Lortab) (Thomas McLellan, 2017).

Impact of the COVID-19 Pandemic on Prevalence and Diagnosis in Mental and Behavioral Disorders Due to Substance

Several studies have revealed that there has been a significant increase in the prevalence of various psychological disorders such as anxiety, depression, stress, and insomnia in the era of the COVID-19 pandemic. When there is an increase in psychological stress, people

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tend to overcome these problems by engaging in addictive behaviors such as substance use, excessive internet use and other addictive behaviors (Dietze et al., 2020; Elhai et al., 2020; Spitzer et al., 2006) This behavior is known as a coping mechanism which is defined as an action to prevent and adjust in stressful situations on theirself and the environment to reduce stress levels (Vaida, Todor, Bertossi, & Corega, 2015). This increase is likely due to several factors, such as the implementation of the quarantine system, physical distancing restrictions, changes in the health care system, and economic difficulties that occur in various countries in the world. These changes in circumstances forced everyone to stay at home, the loss of daily routines and pleasures, and the closure of schools, restaurants, businesses, and entertainment venues, resulting in various concerns such as anxiety and fear of contracting the COVID-19 virus, losing jobs, and other problems. Education will affect a person's mental health (Avena, Simkus, Lewandowski, Gold, & Potenza, 2021; López-Pelayo et al., 2020). This situation is also at risk for making people who previously wanted to stop using substances experience a relapse and tend to increase their use to self-medicate their mental conditions (Dietze & Peacock, 2020).

Based on research by Dietze et al. in the United States in June 2020, it was said that drug use and suicidal ideation had increased, which could affect mental health conditions. In addition, the prevalence of symptoms of anxiety disorders has increased threefold from that reported in the second quarter of 2019 around (25.5% versus 8.1%), and the prevalence of depressive disorders has increased fourfold based on reports in the second quarter of 2017. 2019 (24.3% versus 6.5%) (Dietze et al., 2020). Based on surveys and research conducted by *Perhimpunan Dokter Spesialis Kedokteran Jiwa Indonesia* (PDSKJI), it was found that 1,522 respondents showed mental health problems. Around 64.8% of people experienced anxiety symptoms, depression (61.5%), and past trauma (75%) in Covid-19 Pandemic. A follow-up examination in the second study had 2,364 respondents in 34 provinces was not much different from the first result, with about 68% experiencing anxiety, 67% experiencing depression, and 77% experiencing psychological trauma (PDSKJI, 2020).

Then based on the World Drug Report 2020, obtained from 269 million people who use drugs, there are 35 million people who experience SUD due to substance use. A person with SUD is at higher risk of contracting COVID-19 and having more severe complications. Long-term drug use can put you at risk for cardiovascular problems and chronic obstructive pulmonary disease, which can worsen COVID-19 symptoms and increase the risk of death. Other risk factors for transmission and worsening of COVID-19 symptoms include people with poor immune systems, chronic alcoholics, drug use, blood-borne or sexually transmitted diseases, poor nutritional status, socioeconomic factors, and free sex. Drug users also have a very high risk of COVID-19 (Radfar et al., 2021).

A study conducted by Pollard, Tucker, and Green (2020) found a positive correlation between exposure to stress and alcohol and substance use. The frequency of alcohol consumption among adults in the United States increased by 14% from 2019 to 2020. Then episodes of heavy drinking increased by 41% in women since quarantine (Pollard, Tucker, & Green, 2020).A 2020 study reported that students in Russia who underwent strict quarantine during the COVID-19 pandemic showed a higher increase in alcohol use than students under the supervision of an educational institution (Gritsenko et al., 2020). *American Medical Association* also reported that Between March and May 2020, people who tested positive for fentanyl, methamphetamine, cocaine, and

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heroin increased by 32%, 20%, 10%, and 12%, respectively (American Medical Association, 2020). The analysis also shows that with the quarantine policy during the COVID-19 pandemic, overdose cases increased by 17.59 compared to before the quarantine (Alter & Yeager, 2020).

The diagnosis of mental and behavioral disorders due to substances is made if a history of using substances can cause significant symptoms. Besides that, it is also supported by laboratory tests such as urine or blood specimens. The discovery of other evidence, such as the presence of tools or drugs that were found and the existence of information from the family or the local community, so that the diagnosis of mental and behavioral disorders requires strong evidence (Saunders., 2017).

The application of lockdown during the pandemic for a long time can result in difficulty controlling emotions and mood swings among teenagers, mainly when abusing substances on an ongoing basis. Government efforts to prevent the spread of COVID-19 infection by staying at home, withdrawal can allow a person to hide and use substances. In addition, when a person tries to hide to leave the house with friends, it can be a factor for teenagers to abuse substances. A strange smell in a teen's room can be a sign that you are abusing certain substances, for example, marijuana has a distinct skunk-like odor when smoked, an unusually sweet smell can result from vaping or from sugary drinks mixed with alcohol (Lundahl, 2020).

Interventions and Approaches to Support Mental Health During the COVID-19 Pandemic

The approach is taken to treat patients with mental and behavioral disorders (SUD) because substances are certainly different during and before the COVID-19 pandemic. Due to the many regulations that cause people to have to keep their distance to self-isolation at home, a lack of interaction and social activities leads to other difficulties in terms of economy, religion, etc. This also impacts patients with SUD who find it challenging to do counseling or psychotherapy, gain access to health care or get treatment if symptoms recur or worsen (Marel et al., 2021).

Many studies and journals have discussed attempts at therapeutic approaches in patients with mental disorders to help reduce substance use and prevent suicide during and after the COVID-19 Pandemic (Samhsa, 2021). During the pandemic, the Center for Academic Development in Drug Addiction (CEDRO) of the Medical University of Havana (UCMH) has applied the implementation method of telephone, email, and social networks (especially Whatsapp) to monitor therapy from individuals who want health services. This method is recommended when physical distancing conditions are applied and is very useful in reducing the negative impact on mental health. Findings from Fabelo-Roche, *et al* (2021) show that despite the potential negatives that self-isolation can cause as a preventive activity in times of pandemic, individual coping mechanisms developed by this method in patients. They can increase self-control, allowing to a large extent, to avoid the setbacks that have affected recovery. However, patients have faced various challenges during their recovery period, exacerbated by difficulties in specific situations, myths related to addictive substances and activities, tendencies to think irrationally, or lack of emotional self-control (Fabelo-Roche et al., 2021).

These findings also indicate that patients can face challenges because COVID-19 is influenced by: 1) Individual methods of self-control (commitment to study, projects, and working with therapists) aimed at self-restraint (78.4%);

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2) Facing difficulties in specific opportunities or situations (doubt, uncertainty, disagreement, isolation, and time) (67.5%); 3) Preservation and realization of myths related to addictive substances and activities (poor original benefits of tobacco, marijuana, alcohol, and overuse of social media) (51.3%); 4) Tendency to think irrationally and lack of emotional control (fear, sadness, anger, constant anxiety and self-imposed demands (43.2%) (Fabelo-Roche et al., 2021).

CONCLUSION

The COVID-19 pandemic has a significant impact on various aspects ranging from economic, educational, social, and others that can affect a person's mental health and behavior to be at high risk for substance abuse. Our study found a significant increase in prevalence in people with substance-induced mental and behavioral disorders (SUD) during the pandemic. Therefore, health workers must improve health services so that people with SUD can receive access to the health they need even in a pandemic. The management strategy for substance-induced SUD patients that are carried out digitally and supported by the closest person has proven to be effective even though psychotherapy is carried out remotely during a pandemic.

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Literature review

The relationship between bacterial characteristics and mortality in diabetic foot ulcers' patients admitted to Dr. H. Abdul Moeloek General Hospital, Lampung

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ABSTRACT

Around 25% of people with diabetes experience diabetic foot ulcers in their lives, accompanied by infections due to various types of bacteria. Infection due to Gram-negative and Gram-positive bacteria are reported to have different inflammation patterns, where the latter being reported to have a higher mortality rate. This study was an analytic observational study with a cross-sectional design to determine the relationship between bacterial characteristics and mortality in diabetic foot ulcers. Data were obtained from medical records of diabetic ulcer patients admitted to Dr. H. Abdul Moeloek General Hospital, Lampung, in 2017–2020. There were 131 diabetic foot ulcers patients identified, with the median age of the subjects was 53 years, 43.5% of the subject were male, and 56.5% were female. The mean hemoglobin was 9.3 g/dl, WBCs were 19.0 $\times 10^3$/ml, and platelets were 422.1 $\times 10^3$/ml. The mean length of stay in the hospital was 10.7 days. Eighteen subjects died during the hospital stay, with 15 of them were from the Gram-negative monomicrobial group. The results of the Fischer Exact test on mortality and bacterial characteristics among monomicrobial infections (p=0.688) indicate no relationship between the characteristics of the infectious pathogen and mortality in diabetic foot ulcers.

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INTRODUCTION

A diabetic foot ulcer is the most common complication of diabetes mellitus. Around 25% of patients with DM will develop a diabetic foot ulcer in their lifetime (Jeyaraman *et al.*, 2019). This condition occurs due to a combination of neuropathy, lower leg biomechanical disorders, peripheral artery disease, and poor wound healing due to diabetes (Powers, 2015). A diabetic foot ulcer can be accompanied by infections, ranging from simple superficial cellulitis to chronic osteomyelitis (Amin and Doupis, 2016).

Infection in diabetic foot ulcers is caused by various types of bacteria, whose characteristics depend on the disease's severity and geographic location. In North America and Europe, the main bacteria causing infection in diabetic foot ulcers are aerobic Gram-positive cocci, especially S. aureus and Streptococcus, and coagulase-negative Staphylococcus. Meanwhile, the leading cause of diabetic foot ulcers in tropical/subtropical regions is aerobic Gram-negative bacilli, both as monomicrobial or polymicrobial infection (Lipsky *et al.*, 2020). Mild infection in diabetic ulcers is usually caused by Gram-positive bacteria, while more severe infections usually involve anaerobic and Gram-negative bacteria (Goh *et al.*, 2020).

Infection with Gram-negative and Gram-positive bacteria are reported to have different mechanisms in causing clinical manifestations. Lipoteichoic acid in Gram-positive bacteria and lipopolysaccharides in Gram-negative bacteria cause different host responses, which will result in a different inflammation pattern (Surbatovic *et al.*, 2015). Infection by Gram-negative bacteria has been associated with high morbidity and mortality rates (Blot, 2019; Maskarinec *et al.*, 2020). This study was conducted to determine the relationship between bacterial characteristics and mortality in diabetic foot ulcers based on that analysis.

METHODS

This study was an observational analytic study with a cross-sectional design to determine the relationship between bacterial characteristics and mortality in diabetic foot ulcers. This research was conducted at Dr. H. Abdul Moeloek General Hospital, Lampung Province. The data were obtained from the medical records of diabetic foot ulcers patients admitted to the internal medicine ward of Dr. H. Abdul Moeloek General Hospital, Lampung Province, in 2017–2020. Ethical clearance was obtained from the Medical Faculty of Lampung University and the hospital authority before this study's commencement (Ethical clearance number: 1379/UN26.18/PP.05.02/00/2020).

The subjects of this study were 131 patients meeting the inclusion criteria. The inclusion criteria are the completeness of medical record data, which includes including demographic data (gender and age), laboratory tests (complete blood count, blood chemistry, and pus culture results taken prior to the administration of empirical antibiotics on admission), and clinical outcomes (length of hospital stay and in-hospital mortality). Subjects receiving antibiotics therapy within 72 hours prior to the collection of the pus sample were excluded from this study. The data obtained were analyzed with univariate and bivariate analysis, performed with the Fisher's Exact test. Data were processed with SPSS Statistics v22.0. The test result was considered to be significant if the *p-value* is less than 0.05.

RESULTS

The subjects of this study were 131 patients with diabetic foot ulcers. The characteristics of research subjects are presented in **Table 1**. The median age of the study subjects was 53

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years. The subjects in this study consisted of 57 (43.5%) males and 74 (56.5%) females. Among patients with diabetic foot ulcers, 111 subjects had a monomicrobial infection, and ten subjects had a polymicrobial infection. Gram-negative bacteria were identified in 114 subjects, while Gram-positive bacteria were found in 17 subjects. *Enterobacter spp.* and *Staphylococcus spp.* were the most common Gram-negative and Gram-positive microorganisms found, respectively (shown in **Table 2**). The subjects' median in-hospital length of stay was 10.7 (5.9) days, and 18 (13.7%) subjects died during the hospital stay. The median hemoglobin test result was 9.3 (2.0) g/dl, the median WBC count was 19.0 (7.8) $\times 10^3$/ml, and the median platelet count was 422.1 (170.2) $\times 10^3$/ml.

Table 1. Characteristics of the subjects (N=131)

Characteristics	n (%)	Median (SD)
Median age (years)		53 (31-87)
Sex		
Male	57 (43.5%)	
Female	74 (56.5%)	
Pus culture result		
Gram-positive bacteria	17 (12.9%)	
Gram-negative bacteria	114 (87.1%)	
Length of hospital stay (days)		10.7 (5.9)
In-hospital Mortality	18 (13.7%)	
Hemoglobin (g/dL)		9.3 (2.0)
WBC count ($\times 10^3$/mm^3)		19.0 (7.8)
Platelet count ($\times 10^6$/mm^3)		422.1 (170.2)

Table 2. Bacteria Found in the Diabetic Ulcers based on Microbial Culture (N=131)

Bacteria	Frequency (n)	Percentage (%)
Gram-negative		
Enterobacter spp.	33	25.2
Klebsiella spp.	27	20.6
Proteus spp.	21	16
Pseudomonas spp.	17	12.9
Others	16	12.2
Gram-positive		
Staphylococcus spp.	14	10.7
Streptococcus spp.	3	2.3

Table 3. Relationship Between Bacterial Characteristics and Mortality

	Mortality		*p-value*
	+	-	
Gram-negative	15 (15.3%)	83 (84.7%)	0.688[a]
Gram-positive	1 (7.7%)	12 (92.3%)	

[a]Fischer's Exact test was applied

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The relationship between mortality and bacterial characteristics among diabetic foot ulcers patients with monomicrobial infection was analyzed and is presented in **Table 3**. Based on statistical analysis, it was found that there was no significant relationship between bacterial characteristics and mortality in diabetic foot ulcers patients.

DISCUSSION

The characteristics of an infectious pathogen are reported to influence the mechanism of the host's immunological reaction and the response to therapy (Xu *et al.*, 2013). The microbial infection triggers complex interactions between the pathogen and the host through the introduction of pathogen-associated molecular patterns (PAMP) to the innate immune system. Toll-like receptors (TLR) of the innate immune system are dedicated to the identification of various bacterial components. Lipopolysaccharides, a component of Gram-negative bacteria's outer membrane, will be recognized by TLR-4, while TLR-2 will recognize lipoteichoic acid, a major constituent of the cell wall of Gram-positive bacteria. Depending on the receptors involved, this process leads to the activation of a transcription response program that includes nuclear factor κB (NF-κB), followed by the production and secretion of cytokines, chemokines, and nitrogen monoxide (NO) (Wen *et al.*, 2016). This different mechanism elicited during this process leads to a different pattern of inflammation between Gram-positive and Gram-negative bacterial infections (Surbatovic *et al.*, 2015).

Dysregulated inflammatory response and the production of cytokines have an important role in the development of multiple organ dysfunction in sepsis (Wen *et al.*, 2016). Several studies have shown an association of levels of several cytokines with the severity and outcome of patients with sepsis. Surbatovic *et al.* reported that the levels of TNF-α, IL-8, IL-1ra, and IL-10 were higher in septic patients who died than those who did not (Surbatovic *et al.*, 2015). The cytokine production pattern and initial mediators of inflammation are also believed to depend on the characteristics of the infectious pathogen and the host response. The gram-negative infection has been reported to produce higher levels of TNF-α, IL-6, IL-8, and IL-10, thus higher risk of more severe disease and mortality than Gram-positive infections (Xu *et al.*, 2013).

Our findings showed no relationship between the characteristic of pathogens and mortality in diabetic foot ulcers *(p-value* = 0.688). These findings differ from several other studies that report that the infecting pathogen's characteristics can influence mortality. Pachori *et al.* reported that Gram-negative infections, especially *Pseudomonas spp.*, were associated with a significantly higher mortality rate (Pachori *et al.*, 2019). Another study reported that skin and soft tissue infections in DM patients caused by Gram-negative bacteria had a higher mortality rate than infections caused by Gram-positive bacteria (Benavent *et al.*, 2019). Similar results were also reported by Phua *et al.*, who reported mortality in severe sepsis subjects (Phua *et al.*, 2013). Surbatovic *et al.* and Tabah *et al.* reported higher mortality in sepsis due to infection with Gram-negative bacteria (Tabah *et al.*, 2012; Surbatovic *et al.*, 2015). Meanwhile, our findings were supported by Zahar *et al.,* which reported that the type of infectious pathogen did not affect severe sepsis and septic shock mortality (Zahar *et al.*, 2011). Chotirmall *et al.* and Kushwaha *et al.* also reported that although a positive culture showed a higher mortality rate than a negative culture, the isolated organism's characteristic had little impact on it (Chotirmall *et al.*, 2016; Kushwaha *et al.*, 2020).

One of the essential parts of diabetic ulcers management is antibiotic administration

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(Frykberg and Banks, 2016). Before a culture and antibiotic susceptibility results can be obtained, it is recommended to administer an empiric antibiotic regimen. This empiric antibiotic regimen should cover the most frequently isolated Gram-positive, Gram-negative, and obligate anaerobic bacteria in a local setting (Lipsky *et al.*, 2020). The usage of appropriate empiric antibiotics have been reported to reduce mortality in bacteremia (Gradel *et al.*, 2017; Disselkamp, Coz Yataco, and Simpson, 2019). The implementation of this recommendation could be the reason for the nonsignificant difference in mortality rate between Gram-positive and Gram-negative infections in diabetic foot ulcers. Furthermore, although not significantly different, there was a percentage difference between mortality in Gram-negative (15.3%) and Gram-positive (7.7%)

CONCLUSION

No relationship between the characteristics of the infectious pathogen and mortality in patients with diabetic foot ulcers was found in this study. Further research in multiple centers with a larger sample size should be carried out to confirm the relationship between the two.

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Research Article

Epidemiology of pelvic fracture in the emergency room at Dr. Soetomo General Hospital between 2016-2018

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ABSTRACT

Pelvic fracture is a rare case. The incidence is about 3% to 8% of the whole kind of fractures. The most common cause is high energy trauma and is associated with multi-trauma. The amount of pelvic trauma patients is 63,000 and is associated with increased mortality rates. The scientific data is needed because it is helpful for trauma prevention and management. This research is a descriptive observational study that examines the epidemiology of pelvic trauma. The population was patients with pelvic trauma who came to the ER RSUD Dr. Soetomo in 2016-2018. The total sample was 229 patients. A total of 149 patients (65.1%) were male, and 80 patients (34.9%) were female. Traffic accidents caused 173 patients (76%) cases. Tile A classification was most frequent in 117 patients (51.1%). There were 178 patients (77.7%) who were multi-trauma patients. The most common treatment was pelvic bandage with 95 patients (41.5%). There were 178 multi-trauma patients, 109 patients (61.2%) who underwent emergency surgery for trauma, and 69 patients (38.8%) who did not. The most common cause of pelvic fracture in Dr. Soetomo general hospital during 2016-2018 was trauma with high energy due to traffic accidents. The most common type of pelvic fracture was Tile A. The more severe the pelvic trauma, the treatment should be more aggressive.

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INTRODUCTION

Fracture pelvic is one of the main results of low energy trauma, such as falls, especially in older people. Fracture pelvic is closely associated with morbidity and mortality, with an 8-27% mortality rate of all cases (Andrich *et al.*, 2015). Fracture pelvic has been reported to occur in 3% to 8% of all bone injuries and is often associated with high-energy trauma such as high-speed motor vehicle accidents or falls from heights in younger people. From Epidemiological studies of fracture pelvic, all incidence is 28-37 per 100,000 people for a year (Verbeek *et al.*, 2018).

The main goal of managing fracture pelvic is to reduce the risk of mortality. Severe pelvic trauma can cause significant complications. A recent analysis of more than 63,000 trauma patients showed that fracture pelvic is associated with a high mortality rate (Sathy *et al.*, 2009). There is a significant variability related to risk factors that increase mortality in pelvic trauma. In 15–30%, patients with a high-energy pelvic fracture are commonly unstable hemodynamics. It is directly associated with blood loss due to pelvic trauma. Extensive bleeding is a major cause of death in fracture pelvic (Schulman *et al.*, 2010). The high-power mode of injury is closely related to the mortality rate in fracture pelvic. Several factors influence the prognosis, such as characteristics, diagnosis, and management of fracture pelvic. Therefore, it should be determined immediately to decrease the mortality of these patients. (Breuil, Roux and Carle, 2016). However, there is no data on the incidence rate and characteristics of Dr. Soetomo Hospital and how to handle it in emergency cases.

Therefore, it is important to carry out epidemiological research in orthopedic trauma because epidemiological data can accelerate diagnosis and management that improve the prognosis. This research aimed to describe the distribution of gender, age, the motion of injury (MOI), hemodynamic condition, classification of fracture pelvic, type of injury, and treatment of pelvic trauma patients in Dr.Soetomo general hospital during 2016-2018. In addition, this study aimed to produce scientific data that can be useful for preventing and managing trauma in the population.

METHODS

This research was a descriptive observational study that examines the epidemiology of pelvic trauma. This study population was patients with pelvic trauma who came to the ER RSUD Dr. Soetomo in 2016-2018. This study's sample was a total sampling, all patients with pelvic trauma who went to the emergency room Dr. Soetomo in 2016-2018. The patient characteristics such as gender, age, MOI, hemodynamic condition, classification of fracture pelvic, type of injury and treatment were included in this study. Data of this study was taken from the recapitulation of the patient's medical records. Data was manually collected, and the data were analyzed descriptively; it was first selected, edited, coded, and tabulated. Descriptive data were displayed in tables and graphs and analyzed variables (gender, age, MOI, hemodynamic condition, classification of fracture pelvic, type of injury, and treatment). This study had received Ethical Clearance Information No. 0175/LOE/301.4.2/X/2020 issued by the Research Commission of the Dr. Soetomo Hospital Surabaya.

RESULTS

This retrospective study was conducted with a descriptive design of pelvic trauma profiles in the Emergency Room of Dr. Soetomo Hospital Surabaya in 2016-2018 with a total sample of 229 patients.

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Table 1. Distribution of sample frequencies by gender and age

No.	Characteristic	Amount (%)
1.	**Gender**	
	Male	149 (65.1%)
	Women	80 (34.9%)
	Total	229 (100%)
2.	**Age**	
	0-10	5 (2%)
	11-20	55 (24%)
	21-30	45 (20%)
	31-40	44 (19%)
	41-50	45 (20%)
	51-60	23 (10%)
	61-70	9 (4%)
	>70	3 (1%)
	Total	229 (100%)
3.	**MOI**	
	Traffic Accident	173 (76%)
	Fallen	51 (22%)
	Work accident	5 (2%)
	Total	229 (100%)

According to table 1, out of 229 patients in this study, 149 patients (65.1%) were male, while the remaining 80 patients (34.9%) were female with a ratio of 1.8: 1. The mean patient age was 33.5 years, with the youngest patient was eight years, and the oldest age was 74 years. Traffic accidents are the leading cause of pelvic fractures (76%).

As shown in Table 2, based on pelvic trauma diagnosis classification, most pelvic trauma cases were patients with the Tile A classification, namely 117 patients (51.1%), followed by the APC 2 classification of 26 patients (11.4%). The third most classification of pelvic trauma is the APC 1 classification of 23 patients (10%) and followed by LC 2 classification of 19 patients (8.3%), LC 1 as many as 15 patients (6.6%), Vertical Shear as many as 14 patients (6.1%), APC 3 was ten patients (4.4%) and LC 3 was five patients (2.2%).

Table 3 shows the distribution of the type of therapy based on hemodynamic conditions. Mostly, the patients were 182 patients with stable hemodynamic conditions, 85 patients were subjected to conservative therapy, 83

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patients had a pelvic bandage, 4 patients had C-Clamp insertion, 10 patients had external fixation. 47 patients with unstable hemodynamic conditions, 8 patients received conservative therapy, 12 received pelvic bandage therapy, 17 received C-Clamp insertion, and 10 received external fixation

Based on the type of trauma, from 229 patients, 178 patients, or 77.7% were multi-trauma patients. In contrast, the remaining 22.3% or 51 patients were single-trauma patients. The most common type of comorbid trauma to pelvic trauma was another extremity trauma with 68 cases (38.2%). This study found that the highest number of other trauma surgeries performed by C-clamp installation was in other orthopedic trauma cases, as many as 5 patients out of a total of 14 patients. Meanwhile, the most other trauma surgery that performed external fixation on the pelvis was urogenital trauma surgery with abdominal trauma surgery as many as 4 out of 17 patients. The pelvic bandage was mainly placed on the patient's pelvis, who underwent surgery on other extremities in 19 out of 35 patients. Conservative therapy was mostly performed on patients who underwent surgery in other orthopedic fields, in 16 patients from 35.

Table 2 Distribution of sample frequencies based on the classification of pelvic trauma diagnoses

No	Pelvic Trauma Classification	Amount (n)	(%)
1	**Tile A**	117	51,1%
2	**APC 1**	23	10,0%
3	**APC 2**	26	11,4%
4	**APC 3**	10	4,4%
5	**LC 1**	15	6,6%
6	**LC 2**	19	8,3%
7	**LC 3**	5	2,2%
8	**Vertical Shear**	14	6,1%
	Total	229	100%

Table 3. Distribution of sample frequencies based on the classification of pelvic trauma diagnoses

		Therapy				
		Conservative	Pelvic Bandage	C-Clamp	External Fixation	Total
Hemodynamic	Stable	85	83	4	10	182
Condition	Unstable	8	12	17	10	47
	Total	93	95	21	20	229

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		Treatment				
		C-Clamp	External Fixation	Pelvic Bandage	Conservative	Total
Operations with other trauma	**A**	5	2	19	16	42
	B	0	0	3	3	6
	C	2	1	7	2	12
	D	0	0	2	1	3
	E	1	1	6	2	10
	A+B	0	0	1	3	4
	A+C	1	0	0	0	1
	A+E	3	3	1	4	10
	B+C	0	0	0	1	1
	B+E	0	0	1	0	1
	C+E	1	4	2	3	10
	A+B+E	0	1	0	0	1
	A+C+E	1	2	0	0	3
	A+D+E	0	1	0	0	1
	B+C+E	0	0	1	0	1
	A+B+C+E	0	2	0	0	2
	Total	14	17	43	35	109

*Note
A: Other extremity operation
B: Thorax operation
C: Urogenital operation
D: Head and neck operation
E: Abdomen operation

DISCUSSION

The result of this study is consistent with fracture pelvic epidemiology data in other countries, where most patients are male, and the most common age range is 15-25 years. (Wedel and Galloway, 2013). Another study also obtained similar results where pelvic trauma in men was three times more than in women. This is due to their high participation in physical activities such as construction work, motorbike driving, and other activities. In another study by Eluwa et al., it was also shown that the number of men who experienced traumatic events was greater than that of women. When driving, this might be due to men being often impatient, aggressive, and losing concentration (Eluwa *et al.*, 2010). Also, men have a higher risk of traffic accidents (Young, Birrell, and Stanton, 2011).

Traffic accidents are the most common mode of injury of pelvic trauma in this study. This is also consistent with other studies, which further confirm that pelvic trauma is closely related to high energy trauma (Breuil, Roux and Carle, 2016). This study's results are also in line with research conducted by Ghosh et al., which showed that traffic accidents cause as many as 77% of pelvic trauma. Research conducted by Yang et al. 2014 in Taiwan from 2000 - 2011 also showed that 62% of pelvic trauma causes were traffic accidents. (Yang *et al.*, 2014; Ghosh *et al.*, 2019). Data from the World Report on Traffic Injury Prevention, the death rate due to traffic accidents reaches 1.2 million people each year. The causes of the high number of traffic accidents in developing countries are the steady increase of motorized vehicles, poor enforcement of traffic safety regulations, and

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poor road infrastructure. (Young, Birrell and Stanton, 2011; Organization, 2015)

From the data obtained, 82,1% of patients came with multi-trauma, with about 79,5% stable hemodynamic conditions. The most complicated cases of pelvic trauma in this study were other limb trauma (multiple trauma), in about 38.2%, followed by trauma to other organ systems, which could include trauma to the head and neck, trauma to the thorax, trauma to the urogenital area, trauma to the gastrointestinal area. This result is in line with a study conducted by Yang et al. with 36,594 patients, 23,888 patients experienced multi-trauma, where the most common accompanying trauma was trauma to other extremities in about 60.6%, followed by head injury for 17.6%, and the rest was trauma to thoracic, abdominal and urogenital. Another study in India also obtained similar results where trauma to the other extremities is the most common comorbid trauma to pelvic trauma (Yang *et al.*, 2014; Vidyarthi and Nayak, 2018). An isolated trauma to the pelvis is extremely rare because of pelvic trauma caused by a high-energy injury. High energy trauma transmits the force to the bones and other organs, so pelvic trauma is often accompanied by other accompanying trauma. (Ghosh *et al.*, 2019).

The Tile and Young and Burgess classifications were used to classify each of the pelvic injuries in this study, where these two classifications can be related. Tile A is a stable pelvic trauma condition. Tile B is a partially unstable pelvic trauma condition, where Tile B1 is the same as Young and Burgess APC I and APC II, Tile B2 is the same as Young and Burgess LC I and LC II, Tile B3 is the same as Young and Burgess LC III. Furthermore, Tile C is the same unstable pelvic trauma condition as the Young and Burgess Vertical Shear (VS) and APC III. (Tosounidis *et al.*, 2015). Based on the type of trauma, Tile A (Stable) trauma was the most common type, accounting for 51.1% of the total patients. Whereas for type B Tile, a total of 40.7% of the total patients were obtained, with the distribution for Tile-type B1 as much as 21.4% (APC 1 10% and APC 2 11.4%), Tile-type B2 as much as 14.9% (LC I was 6.6% and LC II was 8.3%), Tile-type B3 was 2.2% (LC III was 2.2%).

Moreover, for Tile Type C, 10.5% of the total patients were obtained (APC III 4.4% and VS 6.1%). This result is in line with a study conducted by Pereira et al. in Brazil where Tile A pelvic trauma was the largest classification of pelvic trauma at 54.5%, followed by Tile B and Tile C pelvic trauma. (Pereira *et al.*, 2017).

In this study, 20 patients (8.7%) had pelvic trauma who underwent external fixation and 21 patients (9.2%) with C-clamp. These results are similar to that of a study conducted by Pereira et al., wherein 9.1% of patients had external fixation, and 7.6% of patients had C-clamp insertion. External fixation provides temporary pelvic ring stability that is rigid and serves as an adjunct to control early bleeding in hemodynamically unstable pelvic ring disorders. External fixation of the anterior via the iliac crest or the supra-acetabular route provides adequate transient pelvic stability in the APC-II / -III and LC-II / -III injury patterns. A posterior pelvic C-clamp may be indicated to control bleeding in vertical shear injuries with sacroiliac joint disorders. Pelvic C-clamp application is contraindicated in communitive and transformational sacral trauma, iliac wing trauma, and type LC pelvic trauma. (Magnone *et al.*, 2014; Weaver and Heng, 2015).

There were some limitations to this study. Firstly, the number of samples was relatively small. Future studies should involve a larger sample size. Secondly, the year span of operation was too short. The length of data is more representative of the real data about the case. Thirdly, this research is a descriptive study

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that is needed to comparison study to improve the study.

CONCLUSION

The most common cause of trauma to the pelvis is trauma with high energy due to traffic accidents. Men had 1.8 times more pelvic trauma than women. Most pelvic trauma types are Tile A. Pelvic trauma patients who experience trauma elsewhere (multi-trauma) are more likely to experience more than just pelvic trauma (single trauma). The more severe the pelvic trauma suffered (see classification), the more aggressive the therapy was. The more hemodynamically unstable the patient, the more aggressive the pelvic trauma therapy was. If an invasive treatment is performed on accompanying trauma in the abdominal and urogenital area, then therapy for pelvic trauma will be more aggressive.

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Research Article

Comparison of subjective and functional results on the operative and non-operative application of clavicle fractures

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ABSTRACT

A clavicle fracture is one of the most common bone injuries occurring in 2-5% of all adult fractures. Clavicle fractures rarely require surgery. Most of the cases were treated by conservative methods. Conservative treatment yields satisfactory results. However, some latest studies showed an incidence of nonunion of up to 15% and patient dissatisfaction of 31%. This study analyzed the outcome and incidence of complications between operative therapy compared to conservative treatment. This research design was a retrospective descriptive observative. The study population was all patients diagnosed with clavicle fracture of the middle third in RSUD Dr. Soetomo Surabaya from 2015 to 2019. The total sample was 153 patients, with 95 patients who underwent conservative measures and 58 patients who underwent surgery. From the results, there were significant differences between the mean SF-36 score [90.81 and 98.21 (p = 0.000)], the mean DASH score [6.94 and 2.42 (p = 0.000)] in patients with fractures clavicle middle third treated with conservative and operative treatment. The union and functional rates were also better in the operative group. This study shows that the operative treatment on clavicle fractures is superior compared to conservative therapy.

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INTRODUCTION

A clavicle fracture is one of the bone injuries that occurs most frequently in 2-5% of all adult fractures, with an incidence of 29-64 cases per 100,000 (Robinson, 1998). Younger individuals often experience these injuries due to high-energy trauma, such as motor vehicle accidents or sports injuries. In contrast, older individuals are more likely to experience injuries due to low-energy trauma such as slips and falls at home (Kihlström et al., 2017).

Clavicle fractures rarely require surgery. Mostly, the treatment was conservative. Most cases of middle third clavicle fractures can be treated with various immobilization methods. Thus conservative therapy is the primary modality in managing these fractures (Naveen, Joshi, and Harikrishnan, 2017). Conservative treatment yields satisfactory results with a high union rate and a relatively low nonunion rate of 0.03-6.2%. However, recent research shows that nonunion incidence is up to 15%, and patient dissatisfaction is 31% (Jha et al., 2018). Conservative treatment can also cause functional disorders of the shoulder and lumps, which are cosmetically unfavorable. Operative management maintaining standard bone length and alignment can prevent the disadvantages of conservative treatment. Good outcomes with high union rates and low complication rates have been achieved with operative modalities. However, operative treatment is not without weaknesses; operative treatment can lead to surgical wound infections, hypertrophic scars, protruding implants, and re-surgery when removing the implants (Naveen et al., 2017).

Orthopedic surgeons still have doubts about the gold standard to treat clavicle fractures, whether operative or conservative therapy. This study analyzed the outcome and the incidence of complications from malunion and nonunion between operative therapy using a plate and screw compared to conservative treatment.

METHODS

This research design was a retrospective descriptive observative. The study population was all patients diagnosed with closed fracture middle third of clavicle in RSUD Dr. Soetomo Surabaya from 2015 to 2019. This study's sample was all patients who met the inclusion criteria. The inclusion criteria were patients with a history of closed fracture in the middle third of the clavicle, both male and female, who have surgery and are treated conservatively at Dr. Soetomo, and were willing to be evaluated. Data were collected at the orthopedic and traumatology polyclinic Dr. Soetomo hospital. Exclusion criteria in this study were patients with a history of fractures other than clavicle fractures, multi-trauma (injury to more than 1 region of the body), communication problems, and refusal to participate in the study. The evaluation time of both groups was one year after the time of the incident. Conservative was mean that the patient treated using arm sling or *ransel verband*. The operative was mean that the patient underwent operation with plate and screw fixation.

Disability of Arm, Shoulder, and Hand (DASH) questionnaire score is an instrument with specific results that are managed and developed as a measuring tool for disability and upper extremity disorders that we can assess for ourselves. DASH consists of 30 items of scoring points, a score of 0 (without disability) to 100 (Gummesson, Atroshi, and Ekdahl, 2003)

The Medical Outcomes Study Short-Form Health Survey (SF-36) is a health status questionnaire developed in two decades to assess patients' functional status and health. SF-36 has been used for various clinical purposes,

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including orthopedics and traumatology (Zhang et al., 2015). The SF-36 is a product of The Medical Outcomes Study (MOS), a four-year study examining specific medical treatment outcomes. Starting from the 149-item Functional and Well Being Profile used by MOS, 20 short survey items named SF-20 were formed in collaboration with RAND Corporation published SF-36 in 1992 (Laucis et al., 2015). SF-36 is a questionnaire containing 36 question items that evaluate the physical function, social function, activity limitations due to physical & mental health, vitality, pain, and general health status (Carreon et al., 2011).

Data of patients of closed fracture middle third of clavicle both have undergone surgery and conservative treatment about subjective and functional outcome data in gender, age, site of injury, dominant hand, DASH Score, SF-36 retrieved from medical records. The collected data were analyzed with SPSS using a non-parametric independent sample test.

RESULTS

There were 531 cases of patients with closed fracture middle third of the clavicle from the database search. The patient with multi-trauma was 182 patients, multiple fractures were 96 patients, and loss of contact was 100 patients. The final data that match the criteria obtained data of 153 patients with clavicle fracture middle third who came to Dr. Soetomo Hospital period January 2015 to January 2019. From the data obtained, 95 patients performed conservative actions, and 58 patients performed operative actions.

Characteristics found that the male sex was 110 people (71.9%), and the female sex was 43 people (28.1%) with a mean age of 35.27 years and a standard deviation of 12.23 years. The most injured clavicle side was on the right side with a total of 105 people (68.52%) and on the left side as many as 48 people (31.48%). One hundred and forty patients suffered from traffic accidents (91,5%). All patients had a right-sided dominant hand (100%). Based on this descriptive analysis, it was found that the comparison of the number of cases handled conservatively, and operatively was quite different, namely 95 people (62.1%) with conservative measures and 58 people (37.9%) with operative measures. These characteristics are shown in table 1.

The data obtained is then performed a normality test to determine the distribution of data. The number of samples from the data above was 153 patients so that the normality test was focused on the Shapiro-Wilk column showing a value below 0.05 ($p = 0.000$). So that the data is normally distributed for the SF-36 and DASH Score data.

Based on table 2, it can be seen that there is a significant difference between the mean SF-36 scores of patients with clavicle fractures of 1/3 of conservative and operative measures. namely 90.81 and 98.21 ($p = 0.000$).

Based on table 3, it can be seen that there is a significant difference between the mean DASH score of patients with clavicle fractures of 1/3 of conservative and operative measures. namely 6.94 and 2.42 ($p = 0.000$).

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Table 1. Characteristics of Patients with Middle 1/3 Clavicle Fracture

Characteristic	Amount (%)
Gender	
Male	110 (71.9%)
Female	43 (28.1%)
Age	
0-18	10 (6.5%)
18-40	125 (81.7%)
40-65	18 (11.8%)
Dominant Hand	
Right	153 (100%)
Left	0 (0%)
Mode of Injury	
Road Traffic Accident	140 (91.5%)
Fall from height	13 (8.5%)
Injury Side	
Right	105(68.62%)
Left	48(31.38%)
Treatment	
Conservative	95 (62.1%)
Armsling	80 (84.2%)
Ransel Verband	15 (15.8%)
Operative	58 (37.9%)

Table 2. Test Results on The SF-36 Based on The Type of Treatment

Treatment	N	Mean	Standard Deviation	p Score
Conservative	95	90.81	4.62	0.000
Operative	58,	98.21	1.1	0.000

Table 3. Test Results on The DASH Score Based on The Type of Treatment

Treatment	n	Mean	Standard Deviation	p Score
Conservative	95	7.01	5.00	0.000
Operatives	58	2.54	4.16	0.000

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DISCUSSION

A clavicle fracture is one of the most common injuries around the shoulder. It has been reported that clavicle fractures account for about 2.6% of all fractures. Men's incidence is usually highest in the second and third decades, decreasing after that with age. In women, it is generally bimodal, with a peak incidence in the young and the elderly. Allman classified clavicle fractures into three groups based on their location along the bone. Middle third fractures are the most common and account for approximately 80-85% of clavicle fractures. The narrow cross-section of the bone in the middle trunk combined with the distinctive muscle force acting on it tends to cause fractures at this location. (Kihlström et al., 2017; Naveen et al., 2017).

The goal of treating a clavicle fracture is to reduce pain and make the patient comfortable. There are two treatments for clavicle fracture, namely operative and non-operative. Indications for surgery in clavicle fractures include open fractures, shortening of more than 20 mm, neurovascular problems, puncture of the skin by the fracture fragments. Non-operative management often uses the arm sling or the figure of eight (Virtanen et al., 2012).

This study illustrated that clavicle fractures are quite frequent, with the incidence in Dr. Soetomo Hospital having about 531 cases between December 2019 to January 2020. After exclusion, the final data that match the criteria for this study is 153 patients. The data found that a total of 95 patients (62.1%) performed conservative measures and 58 (37.9%) with operative measures. There are different indications for each patient before surgery (surgery or conservative) because we need to see the patient as a whole. Factors that affect can include the patient's background, fracture configuration, the patient's general condition whether surgery can be done or not. Most middle 1/3 clavicle fractures generally heal by any method of immobilization. Therefore, non-operative treatment is an acceptable modality for clavicle fracture. This is evidenced by the very low rate of nonunion, which was shown by various previous studies. However, recent studies had demonstrated suboptimal outcomes and very high nonunion rates when conservatively managed shear fractures. Other drawbacks of non-operative treatment are functional disorders of the shoulder and non-cosmetic lump at the neck's base, which may be due to clavicle shortening and excessive callus formation. Surgical recovery can prevent these drawbacks of conservative treatment. Good outcomes and low complication rates have been reported with various surgical modalities of primary fixation of displaced fractures. However, operative care also has its disadvantages, such as infection of the surgery site, hypertrophic scars, protruding hardware, and repeated surgeries for implant removal at certain times. Because middle 1/3 clavicle fractures generally coalesce with most treatment modalities, clinical trials comparing these therapeutic options are rare. Moreover, there is no uniform consensus on the definite treatment options for displaced middle 1/3 clavicle fractures. (Naveen et al., 2017; Ropars et al., 2017)

The data obtained were predominantly male as many as 110 people (71.9%), and female gender, as many as 43 people (28.1%). This is in accordance with studies in several journals, which suggest that clavicle fractures are more common in patients of the male sex. (Sharma et al., 2018; Tamaoki et al., 2017). Our study found a mean age range of 35.27 years, which indicates that most patients were young adults. (Napora et al., 2016)

Previously, the evaluation of postoperative curative effects was primarily based on neurological dysfunction. In recent years, attention has been paid to patient subjective feelings (assessed using the SF-36 and DASH)

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(Zhang et al., 2015). Disability of Arm, Shoulder, and Hand (DASH) questionnaire score is an instrument with specific results that are managed and developed as a measuring tool for disability and upper extremity disorders that we can assess for ourselves. DASH consists of 30 scoring point items, a score of 0 (without disability) to 100 (Gummesson, Atroshi, and Ekdahl, 2003). The Medical Outcomes Study Short-Form Health Survey (SF-36) is a health status questionnaire developed in two decades to assess patients' functional status and health. SF-36 has been used for a variety of clinical purposes, including orthopedics and traumatology. (Zhang, Zhou, and Sun, 2015).

In the evaluation with DASH score, the operative group had significant results with a mean of 2.54 compared to the conservative group with a mean of 7.01. There was also a significant difference between the mean SF-36 score of patients with clavicle fractures of 1/3 of conservative and operative measures, namely 90.81 and 98.21. In the study conducted by Patel, comparing the DASH score in operative patients at the end of the evaluation, the score was 5.16, while in the non-operative group, the result was 6.36. In a randomized controlled trial conducted by Tamaoki et al. in 2017, the difference in DASH scores was not very significant at one-year postoperative evaluation in the operative and conservative groups (Tamaoki et al., 2017). In the Canadian Orthopedic Trauma Society study in 2007, it was found that the DASH score of the non-operative group was 13, while the DASH score of the operative group was better with a score of 5.2 (Zhang et al., 2015).

The function of the clavicle is as a strut and suspensory. The strut is a bridge between the trunk and the upper extremity. The suspension holds the force from the arm as the place where the upper extremity muscles are attached (Owens & Goss, 2006). Therefore the clavicle is very influential on the upper extremities. The AAOS has proposed the DASH score as the standard tool for evaluation of hand and upper limb disability. The value of the DASH score in some common hand conditions was studied (Luc, 2008).

This study shows that the operative action on clavicle fractures shows superiority compared to conservative therapy. Mean SF-36 and DASH scores were better in the surgery-treated group than the conservatively managed group, which was statistically significant. In the past, conservative management was the mainstay of treatment for all clavicle fractures in the middle third, regardless of displacement and comminution, because the clavicle has excellent remodeling power. The conservative treatment with the number 8 bandage acceptably aligns the shifting fragments and yields good functional results (Burnham, Kim, and Kamineni, 2016). However, a recent meta-analysis revealed a higher rate of nonunion for displaced fractures treated non-operatively (15%) than surgically (2.2%) with modern internal fixation techniques. Several recent trials have also revealed a higher incidence of residual pain, nonunion, malunion, shoulder weakness, decreased shoulder endurance, and lower overall satisfaction after non-operative management of middle 1/3 clavicle fracture. (Jarvis et al., 2018).

The existing literature reports two sets of these fracture events: The first is the largest and is associated with an active young population (sports, motor vehicle accidents), while the second is associated with elderly individuals (osteoporotic fractures with simple falls). A direct blow to the shoulder is the most common injury mechanism resulting in a fracture of the middle 1/3 of the clavicle. Since the shoulder is subjected to a compression force from the lateral side, the clavicle and its articulations are the main areas affected when resisting this force. Most (85%) clavicle fractures occur in the middle due to the narrowest and most

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occasional enveloping soft tissue structure (which can help dissipate the injury force) the rarest. In our study, the age group was 20-50 years. The mean age was 35.2 years. The dominant side was affected in 105 cases (68.62%) of 153 subjects. In comparison, the remaining 48 cases (31.38%) had fractures on the non-dominant side, similar to the incidence reported in the literature (Ropars, Thomazeau, and Huten, 2017).

Early mobilization in the surgical group helped the patient to maintain initial shoulder strength and function. In contrast, the conservatively treated patient was immobilized for three weeks, resulting in shoulder weakness and delayed shoulder function. Therefore, functional outcomes measured by SF-36 and DASH scores were better in the surgically treated patients at all follow-ups than in the nonsurgical group (Naveen, Joshi, and Harikrishnan, 2017).

Previous studies in adults have shown higher rates of patient satisfaction after non-operative treatment for clavicle fractures. However, patient-reported satisfaction scores may be higher with early surgical stabilization in some circumstances. A multicenter trial reported better functional outcomes, lower malunion and nonunion rates, and shorter overall time to healing in surgically treated clavicle fractures after plate fixation (Naveen, Joshi, and Harikrishnan, 2017; Jarvis *et al.*, 2018).

Previous studies have analyzed the risk of shoulder dysfunction after conservative treatment, commonly associated with shortening bone segments, bone deformity, loss of strength, and persistent pain. Some studies have observed a smaller number of consolidation defects after surgical fixation compared to conservative treatment. In contrast, other studies have shown a 37% risk of side effects after a surgical procedure may be due to invasion of periosteal structures, which can lead to nerve damage, blood loss, and post-traumatic hematoma, which can delay fracture healing (Ropars, Thomazeau, and Huten, 2017).

Conservative care remains the gold standard in treating simple non-displaced mid-axis clavicle fractures, but surgical intervention is particularly appropriate for displaced fractures and fractures for inactive young adults. If implants and expertise are available, operative treatment can provide satisfactory results and is superior to non-operative care with an excellent surgical technique. Although certain multicenter trials support the use of primary surgical fixation for diaphyseal fractures, this treatment's effect on outcome may not be sufficient to justify surgical treatment for all patients (Burnham et al., 2016).

However, in this study, there is a limitation. There is no more detailed description of the patient receiving operative therapy concerning the methods and tools that might affect the outcome.

CONCLUSION

This study concludes that surgery is better than conservative treatment in the postoperative functional aspects based on the DASH score and SF-36 score.

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Research Article

A biomechanical comparison of midshaft clavicle plate fixation between two screws and three screws on each side of the fractures

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ABSTRACT

The operative management of mid-clavicle fractures with plate and screw fixation is often performed, with either two or three screws on each side of the fracture. This research aimed to compare biomechanical stability on plate and screw fixation of the middle clavicle fracture with two screws and three screws on each fracture side. There were 12 samples of the fractured cadaveric clavicle in the middle and divided into two treatment groups. The first treatment group was given plate fixation and two screws on each side of the fracture, the second treatment group with plate fixation and three screws. Each group was given a repetitive load tensile force of 200 N, and the fracture shift was measured every ten times, 20 times, and 50 times. The statistical analysis showed a significant difference between plate fixation with two screws and three screws on the tensile force's repetition 20 times and 50 times. The lowest average displacement value after repetition of tensile forces is found in fixation with three screws. Biomechanically, the plate fixation system with three screws on each fracture side was more stable than the two screws in the middle clavicle fracture fixation.

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INTRODUCTION

A clavicle fracture is a common injury between 2.6% and 4% of adult fractures and approximately 35% of all shoulder injuries (C Michael Robinson, 1998). Fractures in the middle third of the clavicle are the most common fractures, with a percentage ranging from 69% to 82% of all clavicle fractures (Jeray, 2007; Postacchini et al., 2002). Clavicle fracture management can be performed operatively or non-operatively (Liu et al., 2013). However, nonoperative treatment outcomes are not as favorable as once thought, and the trend to surgically treat these fractures has grown (Hill et al., 1997). The optimal implant for clavicular fixation remains controversial (Kleweno et al., 2011; Narsaria et al., 2014). Plate fixation produces low implant failure rates and more rigid constructs than pins (Duan et al., 2011). One study comparing operative and nonoperative management has shown that plate fixation in middle-third clavicle fractures results in improved functional and lower rates of malunion and non-union (Laursen & Døssing, 1999).

The standard surgical technique for plate fixation in middle-third clavicle fractures involves at least three bicortical screws in the medial and also lateral fragments of the fracture to hold the six cortices on each side of the fracture fragment; however, in some cases, two bicortical screws are used on each side of the fracture fragment. This has led to a debate about the cortex's minimum number held by a screw in each fracture segment (Hak et al., 2010). Several studies compared biomechanical tests between two locking screws and three non-locking screws on each side of the mid-clavicle fracture. However, this is the first study to examine the biomechanical comparison between two non-locking screws and three non-locking screws on each side of the mid-clavicle fracture. This can prove whether the stability of the plate is related to the number of non-locking screws.

METHODS

This research is experimental in vitro study with a randomized control post-test-only group design. This study had been reviewed and received an ethical exemption from the Health Research Ethics Committee, School of Medicine, Airlangga University (No.28 / EC / KEPK / FKUA / 2020). Only clavicles without signs of damage, fractures, or irregularities were included. This study used total sampling with a sample size are 12 cadaveric clavicles were collected from January to March 2020. The cadaveric clavicle was fractured in the middle with a simple (transverse) fracture configuration as samples that met the inclusion criteria, then divided randomly into two groups (each group consisting of six clavicle cadavers), namely the first treatment group (P1) was fixed with two screws on each side of the fracture, the second treatment group (P2) was fixed with three screws on each side of the fracture. The implants used in each group were non-locking one-third tubular plate 3.5 mm with six holes (Ortho Fixor, Shagun Cares, India) and non-locking cortical screws. We designed our biomechanical study to represent this surgical technique because the plate was fixed to the clavicle's superior surface, providing a straighter plate fixation surface. For the P1 group, holding the plate in position on the bone, we drilled three parallel bicortical holes with a 2.5-mm-diameter drill. Screws were inserted between the bone and the plate to apply pullout forces between the plate and the bone and in line with the long axis of the screws. The screws were inserted into all holes (three screws on each side of the fractures) (Figure 1). Each screw was inserted to reach the far cortex. For the P2 group, the same technique and plate type were utilized except that we drilled two parallel bicortical holes with a 2.5-mm-diameter drill

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and inserted two screws into the first and third hole positions on the plate (Figure 1).

Each group compared the displacement of the fracture fragments after fixation and repetitive tensile strength. The shift was measured by comparing the distance between the two points before and after being given a repetitive load-pull using a caliper (Figure 2). The load was given at 200 N, then repeated ten times, 20 times, and 50 times. The load of 200 N represented the maximum force on the clavicle because the most significant force that affects the midshaft clavicle is dynamic muscle force. According to Dyrna research, the muscle that affects the most midshaft clavicle is the deltoid muscle, which is 200 N on approximately (Dyrna et al., 2018; Iannolo et al., 2010). This is why researchers used 200 N for the force tested.

The tools and materials used were the Shimadzu AG-10 TE autograft engine and calipers. The clavicle bone that was fixed with a plate and screw was placed on an autograft machine (Figure 3). Between the two sides of each clavicle, fragments were marked with a dot. Before testing the tensile force, the distance between the two marker points was first measured using a caliper. The pull force of the autograft machine was given a load of 200N and was repeated continuously. The engine pull was paused on the ten times, 20 times, and 50 times repetitions, and measurements were taken at both marker points. This research was conducted at the Special Testing Laboratory of the Faculty of Civil Engineering, Sepuluh November Institute of Technology, and the Laboratory of the Anatomy Department, Faculty of Medicine, Airlangga University.

The collected data will be analyzed statistically using SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). In this study, data were obtained in the form of quantitative data. The normality test was carried out using the Shapiro-Wilk test; if an abnormal distribution was found for each variable, it would be continued with the non-parametric Mann-Whitney test. Statistical significance was defined as $p < 0.05$.

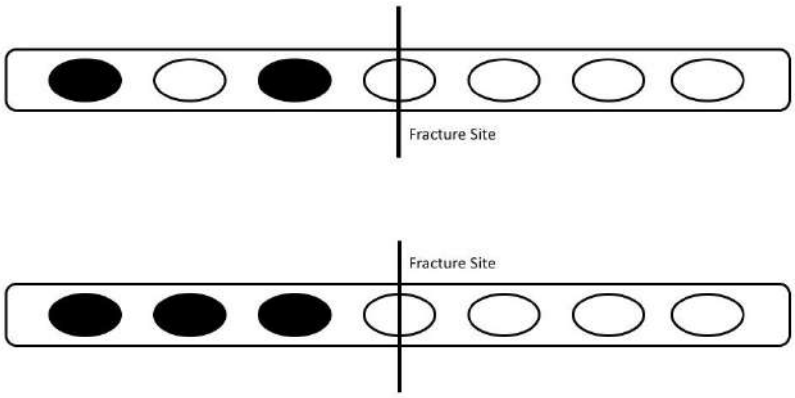

Figure 1. Location for plate application using two non-locking screws and three non-locking screws

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Figure 2. Measurement of the fracture line post tensile test

Figure 3. Clavicle Cadaver in Testing Equipment

Figure 4. Example of the testing process of the clavicle cadaver with Repetitive Load Tensile Force Causing a Fracture Line Shift

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RESULTS

In this study, biomechanical tests were carried out on 12 cadaveric clavicle samples that had met the inclusion criteria. The results found the displacement value of each sample's two marker points on repetitions often ten times, 20 times, and 50 times as shown in Table 1.

This study found that the average displacement value was lower in the fixation with three screws than two screws (Table 2). There was a significant difference between plate fixation with two screws and three screws at the repetition of the tensile force of 20 times ($p = 0.007$) and 50 times ($p = 0.003$). Still, there was no significant difference in the repetition of tensile forces as much as ten times ($p = 0.120$), as listed in Table 2.

Table 1. The shift distance for each sample in the biomechanical test

No.	Sample Name	Information	Ten times (mm)	20 times (mm)	50 times (mm)
1.	1A	*Plate* and two *screws* (1)	10	25	38
2.	1B	*Plate* and two *screws* (2)	10	20	23
3.	1C	*Plate* and two *screws* (3)	8	15	20
4.	1D	*Plate* and two *screws* (4)	10	15	25
5.	1E	*Plate* and two *screws* (5)	10	15	20
6.	1F	*Plate* and two *screws* (6)	5	10	20
7.	2A	*Plate* and three *screws* (1)	0	5	10
8.	2B	*Plate* and three *screws* (2)	5	10	10
9.	2C	*Plate* and three *screws* (3)	0	8	10
10.	2D	*Plate* and three *screws* (4)	10	10	15
11.	2E	*Plate* and three *screws* (5)	10	10	15
12.	2F	*Plate* and three *screws* (6)	5	10	15

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Table 2. The biomechanical tests analysis between fixation with two screws and three screws on the repetition of load tensile forces as much as ten times, 20 times, and 50 times

Repetition	2 screws (n = 6)	3 screws (n=6)	P-value
Ten times	8.83 ± 2.041	5.00 ± 4.472	0.120
20 times	16.67 ± 5.164	8.83 ± 2.041	0.007*
50 times	24.33 ± 7.005	12.5 ± 2.739	0.003*

Values are presented as Mean ± SD (standard deviation).

Significant if p value < 0.05

*significant value ($p < 0.05$)

DISCUSSION

Not surprisingly, the middle third is the most common site of clavicle fracture because it is the thinnest and narrowest part of the bone. It is the transitional area of the bone in curvature and lateral anatomy, making it a mechanically weaker area, and is the only area in the clavicle with no ligaments or muscle support. The indications for operative reparation of midshaft clavicle fractures expand; there is a clinical necessity to elucidate differences in biomechanical constancy among different operative procedures and implants used for fracture fixation to provide optimal stability. Compression plates and investigated the role of either superior or anterior-inferior plate location on fracture fixation biomechanics affect operative therapy (Celestre et al., 2008). The clavicle's biomechanics are six directions: tension-compression, torque, superior-inferior, and anterior-posterior (Iannolo et al., 2010).

Fixation stability is an essential concern for bone fracture treatment (Ye et al., 2015). Operative treatment has been recommended for displaced midshaft clavicle fracture (C M Robinson et al., 2013) because of the various problems that can occur with nonoperative treatment, including pain, instability, difficulty in daily care due to multiple trauma, and high non-union rates in cases of severe displacement and initial shortening > 2 cm (Altamimi & McKee, 2008; Smekal et al., 2009). One study stated that operative therapy with open reduction and plate fixation is a reliable method for diminishing the risk of non-union after displaced midshaft clavicular fracture (Society, 2007; Zlowodzki et al., 2005). Another study comparing operative and nonoperative management has shown that plate fixation in middle-third clavicle fractures results in improved functional and lower rates of malunion and non-union (Laursen & Døssing, 1999). Until recently, the cortex's minimum number held by a screw in each fracture segment was still a matter of debate (Hak et al., 2010). However, according to Thyagarajan, the operative management of using plates in the middle of the third clavicular fracture requires at least three bicortical screws on each side of the fracture (Thyagarajan et al., 2009).

This study aims to compare plate fixation stability between two non-locking screws and three non-locking screws on each side of the midshaft clavicle fracture. This study shows that the plate fixation with three non-locking screws is more stable than two non-locking screws. A previous study compared stiffness,

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yield, and ultimate load between fixation with two screws locking compared with three non-locking screws on each side of the fracture in the middle third clavicle fracture with cyclic load testing and in-line pullout testing found no meaningful difference (Grawe et al., 2012; Larsen et al., 2017). Another study showed that the two screws' stiffness was 20% lower than the three screws constructs on the locking plate (Bilmont et al., 2015).

This study still has several limitations. First, research still used a limited type of implants, whereas locking plate implants were widely used in clavicle fracture cases. Second, the number of samples was still small. We hope that there will be better studies with more extensive sampling and more varied use of implants in the future.

CONCLUSION

According to the biomechanical test results, the plate fixation system with three non-locking screws on each side of the fracture was more stable and significantly different from the two non-locking screws in the middle clavicle fracture fixation. Plate fixation with three screws on each side of the midshaft clavicle fracture is an alternative fixation with better stability than the fixation of two screws on each fracture side.

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Research Article

The success of glaucoma therapy in diabetes mellitus and non-diabetes mellitus

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ABSTRACT

Glaucoma is a disease marked with damage to the optic nerve, chronic and can cause blindness. Glaucoma needs regular therapy to prevent blindness. This study was an observational study using a case-control approach. Data were analyzed using the Mann-Whitney test to determine the differences in blood sugar levels in the DM and non-DM groups and the Chi-Square test to determine differences in the success of glaucoma therapy in DM and non-DM patients. There were 66 samples of glaucoma patients in this study, consisting of 14 men (21.2%) and 52 women (78.8%). The mean age of the patients was 61.12 ± 9.17 years. The sample was divided into 2 groups, namely 34 DM patients (51.5%) and 32 non DM patients (48.5%). The Mann-Whitney test showed significant differences in blood sugar levels between the DM and non-DM groups ($p < 0.05$). Blood sugar levels in the DM group were 202.59 ± 73.5 mg / dL and in the non-DM group was 106.19 ± 16.3 mg / dL. In conclusion, there is no difference in the success of glaucoma therapy in DM and non-DM patients.

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INTRODUCTION

Glaucoma is an eye condition that causes global blindness. It is the third blindness after uncorrected refractive error and cataract. Glaucoma contributed 8,49% to the world blindness among adults aged 50 years and older(Cvenkel & Kolko, 2020). Glaucoma is characterized by progressive optic nerve damage, retinal ganglion cells death, and corresponding visual field defect with a relative increase in intraocular pressure as one of the risk factors(Gauthier & Liu, 2017); (Tripathi Shweta, 2020); (Cvenkel & Kolko, 2020).

Glaucoma is an incurable disease that can be controlled with therapy. Glaucoma therapy aims to prevent vision loss, disability, and blindness by controlling intraocular pressure (IOP). IOP is the principal knew and a modifiable risk factor for the development and progression of glaucoma. The success of therapy in glaucoma can be seen from the intraocular pressure that matches suitable with the therapeutic target (≤ 20 mmHg) or lowering by 20-40% of IOP (Rizka et al. 2020); (Cvenkel & Kolko, 2020). Generally, glaucoma treatment can use drugs with eye drops or oral medications. Five groups of IOP-lowering eye drops have varying mechanisms of action. Some drops, such as β-blocker and α-2 agonist, have potentially serious systemic side effects. Acetazolamide is the only available oral agent, it is effective at lowering IOP, but significant side effects relegate its use, usually to refractory glaucoma. Selective laser trabeculoplasty is a gentle treatment that enhances conventional aqueous outflow. Trabeculectomy is the gold standard surgery to lowering IOP (Paul Riordan-Eva, 2018); (Rizka et al., 2020); (Lusthaus & Goldberg, 2019). Glaucoma patients with Diabetes Mellitus (DM) have additional damage mechanisms to the lamina cribrosa and trabecular meshwork, and they have relatively higher intraocular pressure (Costa et al., 2015).

Hyperglycemia in DM can increase Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase. It is the major source of Reactive Oxigen Species (ROS) production (Dos Santos et al., 2019). ROS will increase oxidative stress, which can contribute to the pathogenesis of glaucoma, increase IOP and disturb the endothelial function and make a loss of pericytes (Volpe et al., 2018); (Benoist d'Azy et al., 2016); (Tang et al., 2019); (Kida et al., 2015); (J. Zhao et al., 2016). DM can cause microvascular damage and several disorders of the body's regulation of the retina, optic nerve and increase the susceptibility of ganglion cells to oxidative stress damage in glaucoma such as increased intraocular pressure (Torres-Martínez et al., 2016). Therefore, this study aimed to determine the differences in the success of glaucoma therapy in DM and non-DM patients.

METHODS

This study was an observational study using a case-control approach with the ethical clearance number 038/EC-EXEM-KEPK FKIK UMY/IV/2020. The study sample was glaucoma patients with a history of DM, and as control was glaucoma patients non-DM. The data was taken from patients' medical records at Purbowangi Gombong Hospital, Kebumen Eye Center Clinic, and PKU Muhammadiyah Gamping Yogyakarta Hospital from November 2019 to August 2020.

Sampling from this study using a simple random sampling technique. The inclusion criteria in this study were glaucoma patients who were routine visited hospital to take medicine, male or female aged more than 40 years, with routine treatment for at least one year, with a history of Diabetes Mellitus at least 5 years.

Non-DM glaucoma patients were taken as controls. The exclusion criteria were glaucoma

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patients with normotension type glaucoma and secondary glaucoma (including neovascular glaucoma), glaucoma patients who were pregnant, glaucoma patients with a history of glaucoma surgery and other eye surgeries and Diabetes Mellitus patients with severe complications such as heart disease and kidney failure. The success of glaucoma therapy was seen from the level of Intra Ocular Pressure (IOP). It was said to be a success if it meets the IOP therapy target ≤ 20 mmHg and was said unsuccess if IOP> 20 mmHg. The Data were analyzed using Chi-Square by SPSS to determine differences in the success of glaucoma therapy in DM and non-DM patients.

RESULTS

In this study, 66 samples of glaucoma patients were collected, consisting of 14 men (21.2%) and 52 women (78.8%). The mean age of the patients was 61.12 ± 9.17 years. The sample was divided into 2 groups, namely 34 DM patients (51.5%) and 32 non DM patients (48.5%).

Table 1. Characteristics of subjects based on gender

	Variable	Frequency	Presentage(%)
Sex	Male	14	21.2
	Female	52	78.8
	Total	66	100

Table 2. Characteristics of subjects based on DM status

Variable	Frequency	Percentage(%)
DM	34	51,2
Non DM	32	48,5
Total	66	100

Table 3. Average blood sugar levels and Intra Ocular Pressure (IOP) of the DM and non-DM groups

Parameter	DM (n=34)	Non DM (n=32)	p
Fasting blood sugar levels (mg/dL)	202,59±73,5	106,19 ± 16,3	p < 0,05
IOP (mmHg)	17,94 ± 7,1	17,41± 7,74	p > 0.05

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Table 4. The success rate of glaucoma therapy on DM status in the right and the left eyes

	Glaucoma therapy succeed (IOP≤20)	Not successful (IOP>20)	Total	p
DM	51	17	68	
Non DM	46	18	64	>0,05
Total	97	35	132	

Table 3 shows the mean blood sugar levels and Intra Ocular Pressure (IOP) of the right and left eyes of the DM and non-DM groups. The Mann-Whitney test showed significant differences in blood sugar levels in the DM and non-DM groups ($p < 0.05$). Blood sugar levels in the DM group 202.59 ± 73.5 mg / dL and in the non-DM group and 106.19 ± 16.3 mg / dL. Although the two groups showed significantly different blood sugar levels, blood sugar levels in the DM group showed a not too high increase in blood sugar levels. The patient can control routine blood sugar levels either by diet, exercise, or taking DM drugs.

The mean Intra Ocular Pressure (IOP) of the right and left eyes of glaucoma patients did not show a significant difference ($p > 0.05$) between the DM and non-DM groups. The intraocular pressure in both groups showed a pressure of ≤ 20 mmHg, meaning glaucoma therapy was successful. Even so, the DM group showed a higher Intra Ocular Pressure than the non-DM group, but both of them were still on target therapy (IOP ≤ 20 mmHg).

The success of glaucoma therapy (right and left eyes) in the DM and non-DM groups, as shown in tables 4 and 5 above, with the Chi-Square test, did not show a significant difference ($p > 0.05$), meaning that they were equally successful.

DISCUSSION

Glaucoma is an eye disease that causes blindness. Glaucoma requires regular therapy to prevent blindness. The success of glaucoma therapy is indicated by the decrease in IOP reaching ≤ 20 mmHg. Several factors influence and obstruct the success of glaucoma therapy.

Diabetes Mellitus is the risk factor of glaucoma (Y. X. Zhao & Chen, 2017). Meta-analysis study reported Relative Risk (RR) effect DM to glaucoma 0,65 – 4,2 (Y. X. Zhao & Chen, 2017); (D. Zhao et al., 2015); (Y. X. Zhao & Chen, 2017). The prevalences glaucoma in DM are 6,8 – 15,6% (Beena et al., 2020); (M et al., 2017); (Dharmadhikari et al., 2015) and in Primay Open Angle Glaucoma (POAG) is 20% (Jayanta et al., 2017).

Andrey G et al., (2020) said that DM is associated with elevated IOP but has no clear association with POAG.

Many hypotheses have been offered it. The first theory suggests that long-standing hyperglycemia might increase the risk of neural stress damage. A second theory is that diabetic eyes have a dysregulation in blood flow due to retinal vascular endothelial cell dysfunction. Another explanation might be a remodeling of the connective tissue of the optic nerve head and dysregulation at the trabecular meshwork and the lamina cribosa. In accordance increased IOP and more significant mechanical stress on the optic nerve head.

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Glaucoma in DM (with hyperglycemia condition) is suspected of obstructing the success of glaucoma therapy. Hyperglycemia can increase Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase. It is the major source of Reactive Oxigen Species (ROS) production(Dos Santos et al., 2019). ROS will increase oxidative stress, which can contribute to the pathogenesis of glaucoma, increase IOP and disturb the endothelial function and make a loss of pericytes (Volpe et al., 2018);(Benoist d'Azy et al., 2016); (Tang et al., 2019); (Kida et al., 2015).

In this study, the success of glaucoma therapy in the DM and non-DM groups did not show a significant difference. DM patients may have fasting blood glucose levels that are not too high (202.59 ± 73.5 mg / dL). It is possible for the patient to control routine blood sugar levels either by diet, exercise, or taking DM drugs. From the interviews conducted, most DM patients control and routinely seek treatment to treat their disease.

Patients who receive routine diabetes medication do not appear to be detrimental to the success of glaucoma therapy. The relationship of DM and anti-DM drug to glaucoma remain unclear. It might be the neuroprotective effect of anti-DM (particularly metformin), but there are poorly understood and should be studied (Hou et al., 2019).

The mean Intra Ocular Pressure (IOP) of the right and left eyes of glaucoma patients did not show a significant difference ($p > 0.05$) between the DM and non-DM groups. The glaucoma patient group with DM showed a higher IOP than the non-DM group, but both of them were still on target therapy (IOP ≤ 20 mmHg). Constancy in using drugs and constancy to visits to health services are factors for the success of glaucoma therapy (Rizka et al., 2020).

In glaucoma patients who have good constancy will affect the success of glaucoma therapy. Patients who routinely seek treatment will increase the success of treatment which is indicated by IOP ≤ 20. Communication factors, patient knowledge, health facilities, individual factors, family support, social and health workers affect the level of patient compliance (Rizka et al., 2020).

The results of this study are not in line with research conducted by (Baisakhiya et al., 2017); (Pimentel et al., 2015); (Hanyuda et al., 2020) and (Rizka et al., 2020), who stated in their research that there was a significant influence between blood sugar levels with increased IOP. The study noted that blood sugar levels affected IOP in both DM and non-DM patients. Choudhary and Sinha, 2019 reported that the first mean IOP was higher in the DM group than the non-DM group and the second mean IOP was higher in the uncontrolled DM group than the controlled DM group. A study by Pandey and Tiwari, 2020 showed significantly higher IOP in a patient with type 2 DM than non DM.

In the study of (Lavaju et al., 2017), the results are following this study, it showed there is no effect between DM and IOP on glaucoma. In this study, the results of significance (p) = 0.757 and it was stated that the prevalence of DM in glaucoma patients was 27.4%. In this study, it was noted that patients routinely take anti-glaucoma drugs, so this can cause a decrease in the IOP number in patients. The reduction in IOP in the patient indicates that there is a successful treatment for glaucoma. This study used a cross-sectional method with 113 patients with type 2 diabetes and 76 patients without diabetes.

Desai *et al.*, 2018 research results stated no significant effect between blood sugar levels and TIO. This study says that the impact of DM on glaucoma is still controversial, in several studies showing that the eyes of people with diabetes have decreased ability to regulate blood flow so that it can cause hypoxia and

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respond to increased Intra Ocular Pressure (IOP) in the eyes. However, this study states that the decrease in Intra Ocular Pressure (IOP) can be caused by the influence of routine glaucoma therapy performed by patients.

Another study, Hou *et al.*, 2019 with a total of 197 eyes (55 eyes with type 2 Diabetes Mellitus (DM) in POAG and 142 without type 2 DM in POAG) compare the rates of visual field (VF) loss and retinal nerve fiber layer (RNFL) thinning in both groups. It concluded that there was no statistically significant difference between the two groups, although POAG patients with treated type 2 DM had significantly slower rates of RNFL thinning than those without diagnosed DM. Li *et al.*, 2020 studied in Primary Close Angle Glaucoma (PACG), and it concluded that oxidative stress was involved in the onset and development of PACG. It can be shown that increased Malondialdehyde (MDA) levels were associated with VF progression in a patient with PACG. MDA level is the primary indicator of lipid peroxidation. It is used as the predictor of oxidative stress. MDA level in a patient with glaucoma is higher than usual (Javier & Martinez, 2017).

Several factors cause the hypothesis in this study not to be proven. Blood sugar levels in DM patients were well controlled, as seen from the mean blood sugar levels of 202.59 ± 73.5 mg / dL. It is possible for the patient to take regular diabetes medication or maintain blood sugar levels with diet and exercise. DM patients with controlled blood sugar levels have the same glaucoma therapy success as glaucoma patients without DM. There is a limitation of this study. This study was a retrospective study; therefore, we could not control the routine medication of the sample.

CONCLUSION

From this research, it can be concluded that there is no difference in the success of glaucoma therapy in DM and non-DM patients. DM patients with controlled blood sugar levels will not interfere with the success of glaucoma therapy.

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Research Article

Shallot (*Allium cepa* L.) skin ethanol extract neutralizes liver oxidative stress in diazinon-induced Wistar rats

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ABSTRACT

Diazinon has a hepatotoxic effect since it is metabolized in the liver involving Kupffer cells (KCs) activation, increasing reactive oxygen species (ROS). The flavonoids contained in shallot (*Allium cepa* L.) skin act as antioxidants neutralizing oxidative stress. This study aims to determine the effect of shallot skin ethanol extract (SSEE) on liver MDA level and activated KCs histopathology. The total flavonoids level of SSEE was measured using the aluminum chloride colorimetric method and resulted in 228.1 mg QE/g. Rats were divided into normal, diazinon, and SSEE groups. Diazinon was administered at a dose of 40 mg/kg b.w. for 7 days, followed by SSEE at the dose of 600, 900, and 1,200 mg/kg b.w. for 7 days. Liver malondialdehyde (MDA) level was measured using the MDA-TBA method. The results revealed that diazinon increased liver MDA level ($p < 0.05$), while SSEE at doses of 900 and 1,200 mg/kg b.w. decreased liver MDA level equal to normal ($p > 0.05$). Activated KCs in the SSEE group at a dose of 1,200 mg/kg b.w. was impressively equal to the normal group. In conclusion, SSEE at dose of 1,200 mg/kg b.w. neutralize liver oxidative stress due to diazinon indicated by the decrease of liver MDA level and activated KCs equal to normal.

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INTRODUCTION

Diazinon is an organophosphate pesticide that is widely used by farmers. The usage of diazinon has been banned in the USA since 2004 because it endangers human health. Nevertheless, Indonesian farmers still use diazinon to get rid of pests in order to increase crop productivity (Agency for Toxic Substance and Disease Registry (ATSDR), 2018; Direktorat Pupuk dan Pestisida, 2016). It is estimated that at least 200,000 people worldwide die because of organophosphate poisoning each year (Eddleston, et al., 2008). In 2008, in the amount of 76.47% of all respondents at Sumberejo, Magelang got the decrease of blood acetylcholinesterase level indicating organophosphate poisoning. It happened through ingestion, inhalation, or absorption (Utami, Dangiran, & Darundiati, 2017).

Diazinon has a hepatotoxic effect related to the liver as the main site of its metabolism. It increases free radicals in liver tissue and decreases endogenous antioxidants amount and capacity (Elersek & Filipic, 2011). The previous studies revealed that diazinon increased liver malondialdehyde (MDA). Diazinon also attenuated liver function showed by the increase of alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin. It induced liver structure damage such as rupture in hepatocytes, vacuole formation in the cytoplasm, necrosis, enlargement of sinusoids, and blood vessel congestion with hemorrhage (Al-Attar, Elnaggar, & Almalki, 2017; Wisudanti, Herdiana, & Qodar, 2019).

One of the cells playing a crucial role in liver homeostasis and the pathogenesis of liver injury are Kupffer cells (KCs) (Kolios, et al., 2006; Owumi et al., 2014). KCs are non-parenchymal liver cells, approximately 15% of the total liver cells, and located in the sinusoidal lining of the liver. They constitute the resident tissue macrophage in the liver and 80-90% of the tissue macrophages in the reticuloendothelial system (Dixon et al., 2013; Kolios et al., 2006). They are the first-line defense to be exposed to substances absorbed from the gastrointestinal tract. They eliminate and detoxify foreign pathogens such as toxic agents (Kolios et al., 2006). Toxic agents-induced liver injury releases various signaling molecules activating KCs, which are capable of generating ROS production (Gandhi, 2012; Kolios et al., 2006; Nguyen-Lefebvre & Horuzsko, 2015; Sato et al., 2016).

The increase of free radicals caused by diazinon and KCs activation can be neutralized by antioxidants contained in plants such as shallot (*Allium cepa* L.). The flavonoid quercetin is actually found at the highest level on its skin. Isolated quercetin of shallot skin has 3-5 times higher levels than the edible part (Skerget, et al., 2009). Jung, et al. (2011) reported that quercetin in shallot skin decreased liver MDA level in streptozotocin-induced rats. Nonetheless, consumption of shallot skin is still uncommon, and it is only considered as household and industrial waste.

Flavonoids contained in shallot skin have an essential role as an antioxidant by reducing ROS production related to its scavenging capacity (Vásquez-Espinal et al., 2019). We used liver MDA level as a parameter to represent the effectivity of flavonoids to decline free radicals in the liver because of its presence as the final product of lipid peroxidation. MDA level is also more accurate to measure since it has a longer half-life and stable structure than the other free radicals (Suryadinata, Bambang, & Adriani, 2017). There has not been a study analyzing the effect of shallot skin on liver oxidative stress due to diazinon. Based on the explanation above, the researcher is implicated in determining the antioxidant effect of shallot

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skin ethanol extract (SSEE) on the liver MDA level and activated KCs histopathology in diazinon-induced Wistar rats.

METHODS

The Preparation of Simplicia and SSEE

The shallot skin was elicited from the industrial waste of the fried shallot factory located at Silo, Jember. The variety/species of shallot determined by the Botanical Laboratory of Math and Science Faculty, University of Jember was Biru Lancor (*Allium cepa* L. var. ascalonicum Back). The shallot skin was washed using NaCl 2% and subsequently sun-dried. The dried shallot skin was ground to get Simplicia powder. A total of 600 g of Simplicia powder was put into a jar, and 3 L of 96% ethanol was added and soaked for the first 24 hours with occasional stirring. The filtrate was separated from its solvent by filtration paper. The process was repeated three times. The total filtrate was concentrated using a rotary evaporator at a temperature of 60°C *(Elsyana & Tutik, 2018)*.

The Measurement of Total Flavonoids Level

Chemical Analysis Service Unit measured total flavonoids level, the University of Jember with analysis number registration 02/CASU/III/2021 using aluminium chloride colorimetric method according to the method of Chang et al. (2002). Quercetin was used as standard to calculate the calibration plot (y = 0.0834x + 0.0107, R2 = 0.998).

Animals and Treatment

As a research subject, 25 male Wistar rats aged 2-3 months and bodyweight 150-250 g were randomly divided into five groups consisting of normal, diazinon, and SSEE groups. On days 1 to 7, the normal group was administered corn oil orally, while the rest of the groups were administered diazinon 40 mg/kg b.w orally. On days 8 to 14, the normal and diazinon group received DMSO 3% orally, and the treatment groups received SSEE 600, 900, and 1,200 mg/kg b.w. Orally, respectively. The surgical procedure was carried out immediately to take the liver out for MDA level measurement and histopathological slides preparation. The study was approved by The Ethical Committee for Research, Faculty of Medicine, the University of Jember, with reference number 1465/H.25.1.11/KE/2021.

The Measurement of Liver MDA Level

Liver MDA level was measured using thiobarbituric acid. The liver was washed using Phosphate Buffer Saline (PBS), pH 7.4. As much as 1 g of liver tissue was homogenized with 1 mL of ice-cold NaCl using cold mortar, followed by centrifugation 6000 rpm for 30 minutes. An amount of 550 µL sterile aquadest, 100 µL TCA, 250 µL HCl 1 M, and 100 µL Na-Thiobarbiturat was added to 100 µL supernatant of each sample. The mixture was boiled for 20 minutes and chilled at room temperature. All samples were centrifugated 500 rpm for 10 minutes to get rid of precipitation before being measured at 532 nm wavelength. Liver MDA level was calculated using linear regression equation obtained from a series of standard solution 2.5, 5, 10, 20, and 40 nmol/mL ($y = 66.798x - 6.9041$, $R^2 = 0.9981$) and expressed in nmol MDA per mg liver tissue.

Statistical Analysis

The data of liver MDA level was displayed as mean ± standard deviation. Statistical analysis was performed using the One Way Anova test to analyze the difference between groups, followed by the Least Significant Difference (LSD) post hoc test to analyze the difference of each group compared to others.

Activated KCs Histopathology

The right lobes were soaked in 10% neutral buffer formalin then processed with paraffin. They were cut using microtome with a thickness

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of 3-5 microns then stained using hematoxylin-eosin (HE) for microscopic observation. Liver histopathological slides were observed using LEICA DM500 binocular microscope with a magnification of 400X in five fields of view. The qualitative assessment was focused on activated KCs related to the increase of ROS.

RESULTS

Liver MDA Level

The result of the total flavonoids level of SSEE is shown in Table 1. Total flavonoids level was expressed in mg/g in terms of quercetin equivalent (QE).

The mean liver MDA level is presented in Table 2. The highest mean of liver MDA level was found in the diazinon group, while the lowest mean of liver MDA level was found in the normal group. Among the SSEE groups, the lowest mean liver MDA level was found at a dose of 1,200 mg/kg b.w.

One Way Anova test revealed that liver MDA level was different among groups ($p<0.05$). Diazinon group showed a higher liver MDA level compared to a normal group, yet it was lower in SSEE groups at doses of 900 and 1,200 mg/kg b.w. It was compared to the diazinon group ($p<0.05$) and equal to the normal group ($p>0.05$).

Activated KCs Histopathology

The liver histopathological slides demonstrating activated KCs of each group are presented in Figure 1. Inactivated KCs only showed dense and squamous nuclei; thus, it is difficult to distinguish with endothelial cells. Activated KCs had a wide range of variability in cell shape and size, elongated cytoplasmic processes, and open-face type cells. They were found along the sinusoid and could be observed in contact with other KCs, collagen fibers, and endothelial cells (Basit, Tan, & Webster, 2020). Activated KCs were mostly found in diazinon group; the higher the SSEE dose, the fewer the activated KCs; and activated KCs in the SSEE group at a dose of 1,200 mg/kg b.w. was impressively equal to the normal group.

Table 1. Total flavonoids level

Tested for	Sample code	Test result (mg QE/g extract)
Total flavonoids analysis	SSEE	228.1

Table 2. The mean of liver MDA level

Groups	Mean of liver MDA level ± SD (nmol/mg)
Normal	11.80 ± 2.92^{b}
Diazinon	22.17 ± 5.24^{a}
SSEE 600 mg/kg b.w.	18.39 ± 4.74^{a}
SSEE 900 mg/kg b.w.	13.46 ± 4.29^{b}
SSEE 1,200 mg/kg b.w.	13.32 ± 3.13^{b}

[a]Significant compared to normal group ($p<0.05$), [b]Significant compared to diazinon group ($p<0.05$)

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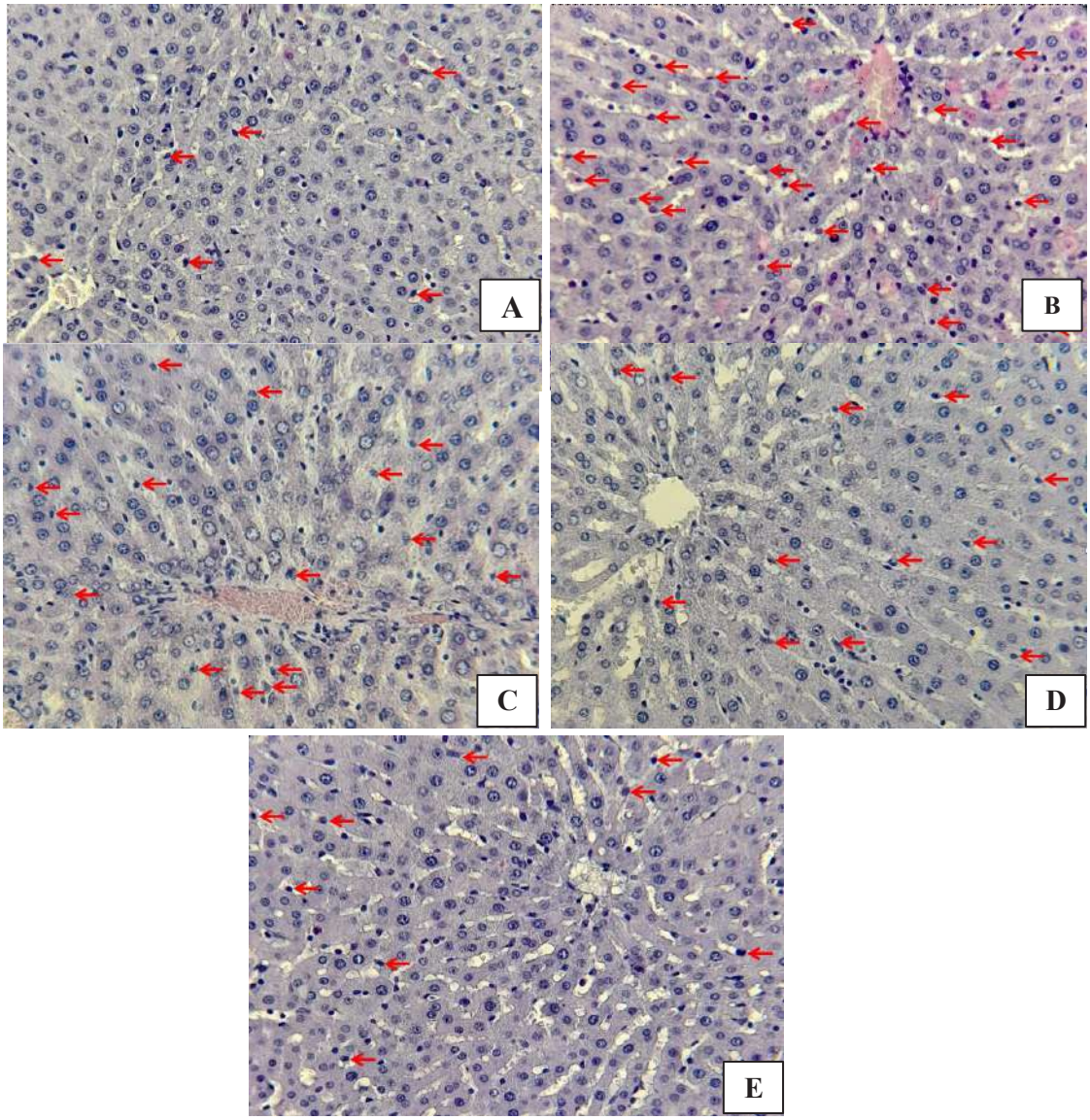

Figure 1. Activated KCs histopathology. A: normal group. B: diazinon group. C: SSEE 600 mg/kg b.w. D: SSEE 900 mg/kg b.w. C: SSEE 1,200 mg/kg b.w. Red arrow shows activated KCs.

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DISCUSSION

The administration of diazinon at a dose of 40 mg/kg b.w. for 7 days could significantly increase liver MDA level. A previous study revealed that diazinon 40 mg/kg b.w administered to rats for 5 days significantly increased liver MDA level (Himah, Wisudanti, & Fatmawati, 2018). Another study reported that diazinon 50 mg/kg b.w. administered to rats for 6 weeks caused liver failure not only indicated by the increase of ALT, AST, total bilirubin, and MDA levels, but also the change of liver histopathological features (Al-Attar et al., 2017)

Diazinon gains the level of free radicals which initiate lipid peroxidation. Diazinon is oxidized to free diazoxon and sulfur atoms by cytochrome P450 (CYP) (Elersek & Filipic, 2011). Diazoxon is a metabolite inhibiting acetylcholinesterase, so that it produces nitric oxide radical (NO•), one of the free radicals formed through the activation of NMDA receptor (Zhao, Vanhoutte, & Leung, 2015). Diazoxon is hydrolyzed by paraoxonase (PON1) to diethyl compounds which can react rapidly with reactive hydroxyl radical group (•OH), resulting in a new free radical (Elersek & Filipic, 2011). Free sulfur atom as a secondary metabolite of diazinon will also bind proton to form H_2S molecule interacting with metalloenzyme such as superoxide dismutase (SOD) then inhibiting its activity (J. Lee, Koo, & Min, 2004). The decrease of antioxidant enzymes inhibits the catalyzation of superoxide-free radical ($\bullet O2^-$) to oxygen (O_2) and hydrogen peroxide (H_2O_2) (Cemeli, Baumgartner, & Anderson, 2009). Excessive free radicals trigger oxidative stress and lipid peroxidation. Lipid peroxidation occurs when polyunsaturated fatty acids (PUFA) in cell membranes or organelle membranes are degraded by free radicals producing lipid hydroperoxide, lipid peroxyl radicals, and MDA as the final product (Ayala, Muñoz, & Argüelles, 2014). In this study, activated KCs were mostly found in diazinon group. KCs are the vital component of the macrophages and specific to the hepatic response to pathogens (Dixon et al., 2013). They are located in sinusoid so that they efficiently phagocytize pathogens entering from the portal circulation (Dixon et al., 2013; Kolios et al., 2006; Sato et al., 2016). KCs are activated by signaling molecule such as interferon-gamma (IFN-γ). When IFN-γ binds to its receptor on macrophages, the signal transducers and activators of transcription 1 (STAT1) and interferon regulatory factors (IRF) are activated, which subsequently cause the activation of KCs (Nguyen-Lefebvre & Horuzsko, 2015). Activated KCs are not only characterized by a high capacity to present antigen, high expression, and secretion of interleukin-12 (IL-12), interleukin-23 (IL-23), and IRF-5, but also high production of NO and ROS as a defense against the toxic agent. Therefore, KCs are capable of generating ROS production (Gandhi, 2012; Kolios et al., 2006; Nguyen-Lefebvre & Horuzsko, 2015; Sato et al., 2016). This theory is supported by Owumi et al. (2014) which stated that KCs depletion reduced cytokines secretion and ROS production, consequently resulting in the amelioration of ethanol-induced liver damage.

The shallot skin contains flavonoids which potentially act as an antioxidant (Mardiah et al., 2017). Shi et al. (2016) isolated flavonoids from dry onion (*Allium Cepa* L.) skin. The flavonoids in $NaHCO_3$ components of diethyl ether phase were isorhamnetin, quercetin, and kaempferol; the Na_2CO_3 component of diethyl ether phase was quercetin-3-O-β-D-glucopyranoside; the Na_2CO_3 components of ethyl acetate phase were rutin and quercetin; the $NaHCO_3$ components of ethyl acetate phase were apigenin-7-O-β-D-glucopyranoside and kaempferol-7-O-β-D-glucopyranoside. Our phytochemical screening showed the total flavonoids level of SSEE was 228.1 mg QE/g. Thus, it should be equivalent to 136.86, 205, and 273 mg QE/kg b.w. total flavonoids for each SSEE group, respectively.

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The first dose of SSEE could not decrease liver MDA level significantly, yet the second and the third doses of SSEE could decrease liver MDA level significantly equal to normal. The response to flavonoid compound is dose-dependent, so that the different doses will result in the different activity of flavonoid in decreasing free radicals (Carmona-Aparicio et al., 2019). Ahmed et al. (2017), investigating the effect of SSEE on liver oxidative stress on CCl_4-induced rats, stated that liver MDA level was influenced by the dose of SSEE. SSEE at a dose of 50 mg/kg b.w. for 17 days could not alleviate liver MDA level while it was significantly decreased at a dose of 100 mg/kg b.w. There were several previous studies adding shallot skin in the rat's diet. The consumption of a diet with 5% shallot skin powder for 4 weeks could significantly decrease liver MDA level and increase SOD, glutathione peroxidase (GSH-Px), and glutathione reductase (GSH-Rx) levels in rats that have an aging process (B. Lee, Jung, & Kim, 2012). The administration of SSEE 1% in the total diet for 8 weeks could significantly decrease liver MDA level on streptozotocin-induced liver injury in rats (Jung et al., 2011).

Quercetin and quercetin 4'-O-β-glucopyranoside constitute the major part of flavonoids in shallot skin compared to others (AbouZid & Elsherbeiny, 2008). The content of flavonoid quercetin in shallot skin is 3-5 times higher than in its bulb (Skerget et al., 2009). A previous study stated that flavonoid quercetin at the dose of 200 mg/kg b.w. could reduce muscle MDA level significantly from ischemia-reperfusion injury in rats (Akdemir et al., 2016). Quercetin decreases the free radical level through radical scavenging mechanisms in its redox reaction, such as hydrogen atom transfer (HAT), sequential proton loss electron transfer (SPLET), and electron transfer-proton transfer (ET-PT) (Vásquez-Espinal et al., 2019). Additionally, quercetin regulates the endogenous antioxidants by modulating the expression of A549 genes, directly increasing the enzyme antioxidants such as GSH-Px, GSH-Rx, and SOD (Boadi, Amartey, & Lo, 2016; Zerin et al., 2013). Thereby, those mechanisms prevent the initial stage of lipid peroxidation (Ayala et al., 2014).

The qualitative assessment of KCs showed the higher the SSEE dose, the fewer activated KCs. SSEE at dose of 1,200 mg/kg b.w. impressively reduced activated KCs equal to the normal group. In this study, SSEE was administered after diazinon induction aimed to analyze its therapeutic effect. Quercetin in SSEE is thought to neutralize the free radical sources mainly derived from diazoxon and the damage of hepatocytes as the result of lipid peroxidation. Hence, the KC's environmental stressors are diminished, and KCs are not further activated. Padma et al. (2012) reported that quercetin decreased hepatic serum markers and MDA as well as improved liver histopathological alteration caused by lindane pesticide toxicity in rats. Hassan, Abo El-Ela, & Abdel-Aziz (2019) stated that quercetin decreases the level of ALT and AST by restoring the histopathological architecture of the liver in imidacloprid insecticide induction in rats. In the other organ, Kalender et al. (2012) showed that the antioxidant effect of quercetin reduced testis MDA level and exhibited milder testis histopathological alterations.

The limitation of this study is that the doses of SSEE are less varied, so that the optimal dose can not be determined. Further research using a wider range of doses is needed to establish the optimal dose of SSEE in neutralizing liver oxidative stress caused by diazinon.

CONCLUSION

In conclusion, SSEE at dose of 1,200 mg/kg b.w. neutralize liver oxidative stress due to diazinon indicated by the decrease of liver MDA level and activated KCs equal to normal.

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Research Article

Correlation between obesity and successful ovulation induction with Clomiphene citrate

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ABSTRACT

Ovulation induction with clomiphene citrate is a hormonal therapy for infertile women with impaired ovarian function caused by dysregulation of the hypothalamus and pituitary, affecting egg development and ovulation. Several factors, such as obesity, influence the success rate of treatment with clomiphene citrate. According to the Asia-Pacific classification, obesity was classified into two categories, obesity type I (25-29,9 kg/m^2) and obesity type II (≥30 kg/m^2). The success rate of ovulation induction with clomiphene citrate in obese infertile women at Graha Amerta Fertility Clinic in Dr. Soetomo General Hospital on July 2019 – July 2020 was about 22.8%. The research aimed to analyze the correlation between obesity with successful ovulation induction with clomiphene citrate. This research method was observational analytic research with a cross-sectional approach. The data were collected from medical records of infertile obese women who undergo ovulation induction with clomiphene citrate. According to inclusion criteria, the number of samples is 79 cycles of infertile obese women who undergo ovulation induction with clomiphene citrate. Data analysis using Chi-square test. The result showed that successful ovulation induction in obese type I was 17.7% and in obese type II was 5.1%. There was a correlation between obesity with successful ovulation induction with clomiphene citrate (p=0.009). In conclusion, there was a correlation between obesity with successful ovulation induction.

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INTRODUCTION

World Health Organization (WHO) describes infertility as the failure to achieve a pregnancy after one year (or more) of regular unprotected sexual intercourse. In Indonesia, infertility affects 10-15% of couples of reproductive age (Harzif et al., 2019). Etiologies of Infertility caused by ovulatory dysfunction (21-25%), tubal factors (14-20%), male factors (30%), and pelvic or uterine abnormalities (10-13%). Ovulation induction is commonly used to treat infertility, specifically anovulation (Lindsay & Vitrikas, 2015). Ovulation induction uses a variety of hormone-based medications. The first-line treatment of patients with anovulation is clomiphene citrate (CC). It is inexpensive, user-friendly because orally administered and doesn't require much monitoring.

Ovulation induction with clomiphene citrate is a hormonal therapy for infertile women with impaired ovarian function caused by dysregulation of the hypothalamus and pituitary, which stimulates egg development and ovulation (Speroff & Fritz, 2012). CC is a selective estrogen receptor modulator (SERM) that has been first line treatment for patient with oligomenorrhea or anovulation more than 40 years. CC mechanism is competing for endogenous estrogen receptors in the hypothalamus and pituitary, reducing negative feedback signaling of natural estrogen. CC binds the hypothalamus longer than natural estrogen, thus making block of the replenishment estrogen receptors. This effect makes the body believe that estrogen level is low, which triggers activation of neuroendocrine to increase release of gonadotropin FSH secretion (Mesiano & Jones, 2017).

CC dosage varies with body weight. Nevertheless, there is no reliable way to predict what dosage will be required in individual women accurately. There are several different management protocols and techniques for CC to allow flexibility and customization of treatment for each patient and provider (Lindheim et al., 2018).

The medications start with a dose 50 mg for 5 days, beginning on day 2-5 of the menstrual cycle or a progestogen-induced menstrual bleed. If ovulation has not occurred, CC dose may be increased up to the maximum dose reached 150 mg or ovulation has occurred (Brown J & Hughes, 2009). Ovulation is expected to occur between day 5-10 after the last CC dose. The success rate of ovulation induction with CC was almost 70-80% of patients, and 40-50% will conceive after six cycles (Balen, 2013). Possibility response decrease is influenced by several factors, such as obesity (Speroff & Fritz, 2012).

Obesity is a common problem among women of reproductive age and is defined as abnormal excessive fat accumulation that negatively affects health (WHO, 2020). According to the Asia-Pacific classification, obesity was classified into two categories, obesity type I (25-29,9 kg/m^2) and obesity type II (≥30 kg/m^2) (Nishida et al., 2004). In obesity, some mechanisms can affect ovulation induction, including increased peripheral aromatization to estrogen, hyperinsulinemia, insulin resistance and hyperleptinemia (Speroff & Fritz, 2012; Oliveira & Lemos, 2010). Obesity also increases the volume distribution of drugs, increasing the total amount of drugs required for the equivalent action at the target organ (Akpinar et al., 2016). All of these factors related to obesity can negatively impact ovulation induction.

In Indonesia, research rarely discusses clomiphene citrate, mainly when it is associated with obesity. This study aims to analyze the relationship between obesity and successful ovulation induction with clomiphene citrate.

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METHODS

This research method is observational analytic with a cross-sectional approach and total sampling technique. The independent variable is obesity, and the dependent variable is successful ovulation induction. This study enrolled 31 obese infertile women with 79 cycles of ovulation induction with CC at Graha Amerta Fertility Clinic in Dr. Soetomo General Hospital from July 2019 – July 2020. The samples in this study were selected according to inclusion criteria. The inclusion criteria of this study were:

1. Obese infertile women who undergo ovulation induction with clomiphene citrate for timed intercourse or intrauterine insemination program
2. The medical record that has ovulation data for each cycle of ovulation induction

Body mass index (BMI) was measured with weight in kilograms divided by the square of height in meters. This study used BMI according to the Asia-Pacific classification because there is evidence that the association between BMI, percentage, and body fat distribution differs between populations. In some Asian populations, a specific BMI reflects a higher rate of body fat than in the white or European population. Obesity was classified into two categories, namely, obesity type I (25-29,9 kg/m^2) and obesity type II (≥30 kg/m^2) (Nishida et al., 2004).

CC induction protocol started with a dose 50 mg (which was increased to 100 and 150 mg in subsequent cycles in case of absence of ovulation) from day 2-5 of menstrual cycles. Once ovulation has occurred, there should be no increasing CC dose. It started from 31 cycles with 50 mg dose, 4 cycles were success. Dose increased to 100 mg for the remaining 27 cycles, and 6 cycles were success. The remaining 21 cycles who did not respond used doses up to 150 mg, and 8 cycles were successful.

Response to ovulation induction with CC were assessed by ovulation. Ovulation was verified by ultrasonography of preovulation follicle size on day 11 up to day 14 cycles greater than 18 mm or the presence of pregnancy. The data were collected and coded then entered into SPSS version 25.0 for windows. Data were analyzed using Chi-square test. The Health Research Ethics Committee section of Dr. Soetomo General Hospital has approved and certified this research with ethical letter number 0036/LOE/301.4.2/II/2021.

RESULT

Table 1 shows the characteristics of the study population. This study enrolled 31 obese infertile women with a total of 79 cycles. The age of study population <35 years were 20 (64.5%) and >35 years 11 (35.5%). Of 31 patients reported experiencing primary infertility were 28 (90.3%) and secondary infertility 3 (9.7%). The number of cycles from infertile obese women who successfully ovulation induction with CC were 18 cycles (22.8%), 14 cycles (17.7%) was obesity type I and 4 (5.1%) were obesity type II.

Table 2 shows the relationship between type obesity and successful ovulation induction using the Chi-square test. There was a significant relationship between obesity and successful ovulation induction p = 0.009.

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Table 1. Characteristics of Study Population

Variable	N	%
Age (years)		
1. <35	20/31	64.5
2. >35	11/31	35.5
Type of Infertility		
1. Primary infertility	28/31	90.3
2. Secondary Infertility	3/31	9.7
Obesity		
1. Obesity Type I	40/79	50.6
2. Obesity Type II	39/79	49.4
Successful Ovulation Induction		
1. Responders	18/79	22.8
2. Non-Responders	61/79	77.2

Table 2. Chi-square test between Obesity and Successful Ovulation Induction

		Successful ovulation induction				Total		P value
		Responders		Non-Responders				
		N	%	N	%	N	%	
Obesity	Obesity Type I	14	17.7	26	32.9	40	50.6	0.009
	Obesity Type II	4	5.1	35	44.3	39	49.4	
Total		18	22.8	61	77.2	79	100	

DISCUSSION

A total of 79 cycles from 31 obese infertile women medical records have been verified as inclusion data from this study. This study found that most responders are the cycles from obesity type I (BMI =25-29,9 kg/m^2). These results are consistent with research conducted by Ellakwa et al., (2016). This study explains that women with higher BMI (≥30 kg/m^2) were less likely to respond to clomiphene citrate. Another study by Aboul et al. (2004). also showed that BMI was significantly higher in CC non-responders patients. These findings indicate that increasing BMI also increases the risk of failure of ovulation induction with CC.

This study demonstrates a significant correlation between obesity and successful ovulation induction with CC (p = 0.009), which is supported by previous reports from Aboul et al., (2004), who found a correlation between obesity and successful ovulation induction with CC (p = <0.001) and information from Ellakwa et al., (2016).with (p = 0.001).

There is evidence that obesity affects ovulation induction. Obese women tend to respond poorly to ovulation induction with CC (Imani et al., 1999).This impact occurred because obesity

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is a predisposing factor of several hormonal changes that play important roles in ovulation, including increased peripheral aromatization to estrogen, hyperinsulinemia, insulin resistance, and hyperleptinemia.

Increased peripheral aromatization to estrogen occurred due to increase the ability of adipose tissue to accumulate sex hormones within adipocytes and interconvert androgens to estrogen through local enzymatic reactions, resulting in elevated estrogen concentrations, which causes negative feedback in the hypothalamus and pituitary, resulting in decreased FSH and anovulation (Oliveira & Lemos, 2010; Rosenfield & Ehrmann, 2016)). Hyperinsulinemia may happen in obese women because increased of body fat changes the sensitivity and pattern secretion of insulin. High levels of insulin can decrease levels of hepatic sex hormone-binding globulin (SHBG) production, resulting in increased levels of free estrogen and testosterone (Speroff & Fritz, 2012). Hyperinsulinemia is also associated with hyperandrogenemia; high insulin levels stimulate androgen synthesis in theca cells, resulting in high local androgen production, which may inhibit ovulation by premature follicular atresia (Nelson & Fleming, 2007). Leptin concentrations are also associated with the amount of adipose tissue so that higher leptin concentrations can be found in obese women. Increased leptin concentrations disrupted follicular development and oocyte maturation (Moschos et al., 2002).

A Study from University of Alexandria, Egypt, showed that women with obesity, hyperandrogenemia, hyperinsulinemia, and high leptin concentrations tend to respond poorly to ovulation induction with CC (Aboul et al., 2004). Obesity also increases the volume distribution of drugs, which increases the total amount of drugs required for the equivalent action at the target organ (Akpinar et al., 2016). Consequently, a higher dose of CC would be required in obese patients compared to non-obese. All of these factors related to obesity can negatively impact ovulation induction with CC.

These study findings have a different result from the Uniformed Services University of Health Sciences, United States, suggesting that CC responders were more obese than non-responders. This occurred because body mass index may not be the most accurate predictor of ovulatory response to CC. This study suggests that the relevant predictor's response was elevated fasting insulin levels in patients who failed to CC (Armstrong et al., 1996). Imani et al., (2000) have designed a nomogram to predict ovulation induction based on patient characteristics. These characteristics contain BMI calculations; calculating BMI is expected to enhance the effectiveness of treatment and cost. Also, BMI can estimate the weight loss needed to improve the responses of ovulation induction. Another study by (2011) revealed that BMI is a predictor of response to ovulation induction agents. Lifestyle modifications and weight loss should always be offered to patients with obesity. Weight loss of 5-10% can cause spontaneous ovulation or increase the response of ovulation induction with CC (Legro et al., 2015).

There are several limitations to this study. First, we evaluated BMI based on the medical record. Therefore our sample size depends on the completeness of data written on the medical record. Second, we could not demonstrate the association between obesity and several hormonal changes that may affect ovulation induction. The only parameter in this study was BMI. Therefore, future research might need other parameters such as insulin resistance, androgen, and serum leptin to demonstrate this relation. Also, this study has a potential bias caused by the fact that each patient could have more than one cycle with a different dose in every treatment. But, with multiple checks of

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the data, we believed we could prevent bias. However, this study is retrospective; a further prospective study is necessary to confirm our result.

CONCLUSION

There was a correlation between obesity and successful ovulation induction with clomiphene citrate. Since obesity may affect ovulation induction, evaluating body mass index parameters is very relevant for infertile women who undergo ovulation induction. Our study suggests that losing weight before starting ovulation induction would improve their reproductive outcomes.

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Research Article

The differences of parasitemia and lungs size in malaria-associated acute respiratory distress syndrome (MA-ARDS) and non-MA-ARDS in mice infected with *Plasmodium berghei* ANKA

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ABSTRACT

Malaria-associated acute respiratory distress syndrome (MA-ARDS) is characterized by extensive infiltration of leukocytes, microhemorrhages, vasogenic edema, changes in lung color, and a significant increase in the weight of the lung. This study was aimed to find out the differences in parasitemia and lung size in MA-ARDS and non-MA-ARDS in mice infected with *Plasmodium berghei* ANKA. Sixteen male BALB/c mice were infected with *P. berghei* ANKA, and daily parasitemia was observed on Giemsa-stained tail blood smears. Mice were sacrificed when parasitemia reached ±20%. Simultaneously eight uninfected mice were used as negative control (NEG). The statistical analysis was done using Kruskal Wallis, Mann Whitney U tests, and Spearman correlation test. The results showed that there were significant differences in parasitemia (p=0.001), weight (p=0.001), and lung length (p=0.021) between the MA-ARDS and non-MA-ARDS groups. Comparison of NEG and MA-ARDS resulted in a significant difference in lung size (p=0.05). When non-MA-ARDS compared with NEG groups, it showed a significant difference in lung width (p=0.001). However, there was no significant difference in lung weight and length (p>0.05). Spearman correlation test showed that there was a strong correlation between parasitemia with weight (p=0.000), length (p=0.001), and lung width (p=0.017). The findings indicated that parasitemia played a role in the development of MA-ARDS in mice infected with *P. berghei* ANKA and influenced the size of the lung.

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INTRODUCTION

Malaria is an infectious disease caused by a parasite of the genus *Plasmodium* and transmitted to humans by the bite of female *Anopheles* mosquito (Heny Arwati, Yotopranoto, Rohmah, & Syafruddin, 2018). In 2020, an estimated 3.2 billion people, almost half the world's population across 91 countries or territories, are still at high risk of malaria (CDC, 2021). It has been stated that malaria will remain a major health problem until 2025 in 107 countries in the world because around 300-500 million people are infected with malaria every year (Dimi, Arlin, & Alim, 2020). Indonesia is one of the countries at risk of malaria because accounting for 21% of the region's reported cases and 16% of malaria deaths (WHO, 2019). The rates of infected population and mortality are still high, especially in Eastern regions such as Papua, West Papua, NTT, Maluku, and North Maluku (Kementrian Kesehatan RI, 2018); however, by 2018, a total of 285 districts in Indonesia successfully achieved their target of eliminating malaria (WHO, 2019).

Malaria-associated acute respiratory distress syndrome (MA-ARDS) is severe malaria with a lethality rate of up to 80% despite anti-malarial treatment. It is characterized by a vast infiltration of leukocytes, microhemorrhages, and vasogenic edema in the lungs (Vandermosten et al., 2018). Approximately 80% of ARDS patients present with fluid around the lungs (pleural effusion) in addition to fluid in the airspaces (alveolar edema) and within the lung parenchyma (interstitial edema) (Melo & Bates, 2019). This disease occurs especially in malaria caused by *Plasmodium falciparum, Plasmodium vivax,* and *Plasmodium knowlesi* (Aisiku et al., 2016). Excessive pulmonary inflammation and alveolar-capillary membrane damage cause overwhelming vasogenic edema and severe hypoxemia (Vandermosten et al., 2018).

Protein-rich pulmonary edema is one of the causes of ARDS that causes severe hypoxemia, and impaired carbon dioxide excretion is associated with large numbers of neutrophils, monocytes; denuded epithelial cells; and proinflammatory markers, including cytokines, proteases, oxidants, and procoagulant factors (Matthay & Zemans, 2011). Accumulation of those cells and formation of edema in the lung contributed to the increased lung weight, and in addition, the total lung weight can be used as a better parameter for the quantification of MA-ARDS (Van den Steen et al., 2013). The color of the lungs of mice infected with *Plasmodium* changed to greyish-brown due to bleeding and increased hemozoin formation (Deroost et al., 2013). Regardless of the *Plasmodium* species, the clinical manifestations of malaria are highly variable, and many factors influence it. The level of parasitemia is related to the severity or malignancy of malaria infection (Avrina et al., 2011). The experimental studies on MA-ARDS in *P. berghei* infection have been reported previously (Vandermosten et al., 2018; Gonzales et al., 2015); however, the differences of parasitemia and lung size in MA-ARDS and non-MA-ARDS in mice infected with *P. berghei* ANKA has not been explored. Pulmonary edema is one of the ARDS signs that caused the increase of lung weight, and parasitemia is an indicator of malaria severity. Therefore, this study was aimed to find out the differences in parasitemia, lung weight, length, and width between MA-ARDS and non-MA-ARDS in *P. berghei* ANKA infection in mice compared with those uninfected mice.

METHODS

Ethical approval

This research proposal has been reviewed and approved by the Ethical Committee from the Faculty of Dental Medicine, Universitas Airlangga, as mentioned on the Ethical Clearance certificate No 159/HRECC.FODM/IV/2021.

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Research Design

This research is an in vivo experimental study with a post-test control group design. Mice were divided into three groups; each group consisted of 8 male mice aged ± 7 weeks and weighing ±25 grams. Group 1 was negative control (NEG) that were not infected with *P.berghei* ANKA; Group 2 and 3 were infected with *P. berghei* ANKA. Group 2 was the MA-ARDS group where mice were expected to develop an MA-ARDS, Group 3 was a non-MA-ARDS group in which mice were without any ARDS symptoms. Observation of lung size was performed at the end of the experiment.

Parasite infection in mice

Parasite *P. berghei* ANKA was obtained from the Department of Medical Parasitology, Faculty of Medicine, Universitas Airlangga. Four healthy BALB/c mice were used as donor mice which were infected with 200µL of frozen blood infected with *P. berghei* ANKA. When parasitemia reached ±20%, the blood was collected by cardiac puncture and infected to the test mice. Each mouse was injected intraperitoneally with $1x10^6$ of infected erythrocytes.

Determination of parasitemia

The degree of parasitemia in donor and test mice was determined daily on Giemsa-stained tail blood smears and calculated based on the number of infected erythrocytes. The smears were examined under a light microscope at 100x magnification. Parasitemia was calculated by the following formula (Laboratory Identification of Parasitemia of Public Health Concern, 2020):

$$\% \text{ Parasitemia} = \frac{\text{Number of infected erythrocytes}}{\text{Total number of erythrocytes counts}} \text{ X } 100\%$$

Determination of MA-ARDS and lung removal

When parasitemia in the infected mice reached >15%, mice were sacrificed, and lungs were removed prior to measurement of their weight, length, and width. The mice were considered MA-ARDS when macroscopically pleural effusion was observed around the lungs, lungs underwent edema and greyish-brown in color (Melo & Bates, 2019; Deroost et al., 2013). The lungs were collected, and the weight was measured using an analytic balance scale, while the length and width were measured using a ruler.

Statistical analysis

The difference between parasitemia and the mice's lung weight, length, and width in the MA-ARDS group was compared with those of non-MA-ARDS and NEG groups by using the Kruskal Wallis test. The comparison between experimental groups was made by employing the Mann-Whitney U test, and the correlation between parasitemia and lung size was determined using the Spearman correlation test. The confidence interval of 95% (α=0.05) was employed, and the results were considered statistically significant when the p-value was less than 0.05.

RESULTS

MA-ARDS and parasitemia

Physical examination of the appearance of mice on the third-day post-*P. berghei* ANKA infection showed that they were still moving actively. However, at day 5 or 6, the mice started to shivering, the four hinds, both ears, and tail were started to be pale and moved less actively. In this appearance, the MA-ARDS-developed mice could not be distinguished from non-MA-ARDS. The observation of mice post scarification found that the chest cavity was full of pleural effusion, and the lungs were

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greyish-brown in color. Only 3 out of 8 mice developed MA-ARDS. The lung color in the MA-ARDS group was virtually different from that of non-MA-ARDS and uninfected mice (NEG), as shown in Figure 1. This figure shows the freshly reddish lung color of the uninfected mouse (A), the greyish-brown of mouse lung with MA-ARDS (B), and dark brown of the non-MA-ARDS mouse (C). Furthermore, observation and counting of parasitemia on Giemsa-stained tail blood smears resulted in the mean of parasitemia in the MA-ARDS group was higher (31.03%) than that of the non-MA-ARDS group (12.51%). Statistical analysis of parasitemia in MA-ARDS and non-MA-ARDS groups was significantly different with p=0.001 (Table 1).

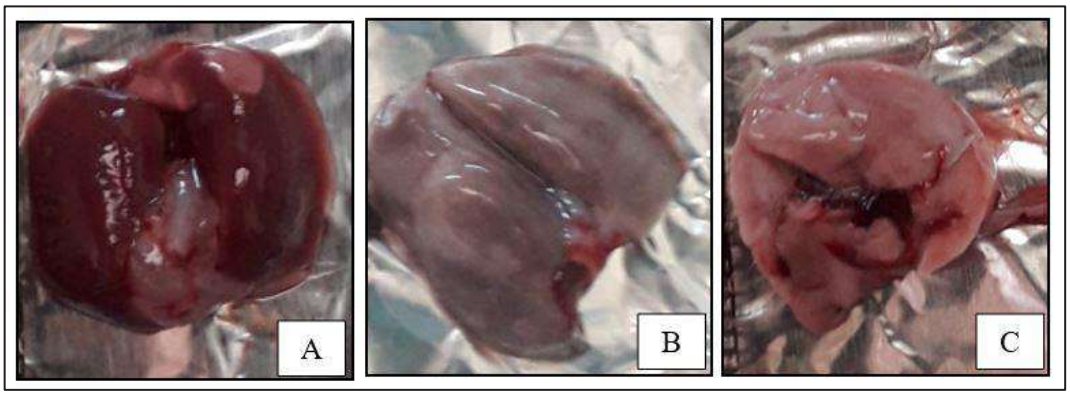

Figure 1. Representative picture of the lungs of mouse infected with *P. berghei* ANKA. The lung of mouse in negative control is freshly reddish (A), in MA-ARDS is greyish-brown (B), and in non-MA-ARDS is dark brown.

Table 1. The differences in parasitemia, lung weight, length and width of MA-ARDS compared with non-MA-ARDS in mice infected P. Berghei ANKA and negative control

	NEGATIVE CONTROL	MA-ARDS	NON MA-ARDS	p*
Parasitemia		31.03±1.68	12.51 ± 1.16	0.001
Lung weight (g)	0.265 ± 0.006	0.343 ± 0.005	0.262 ± 0.006	0.000
Lung length (cm)	1.24 ± 0.056	1.56 ± 0.086	1.30 ± 0.037	0.014
Lung width (cm)	1.18 ± 0.179	1.312 ± 0.047	1.18 ± 0.029	0.001

*Statistical analysis using Kruskal Wallis and Mann Whitney, n=16. Significance p<0.05

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Weight, length, and width of lungs

Comparison of lung size in the MA-ARDS and non-MA-ARDS groups resulted in significant differences in the weight (p=0.001) and length (p=0.021) of lungs; however, the width of the lungs was not (p=0.059). When the size of lungs in MA-ARDS was compared with that in NEG resulted in a significant difference in weight (p=0.001), length (p=0.010,) and width (p=0.005). Further, a comparison of non-MA-ARDS with NEG showed only the width of lungs was significantly different (p=0.001), but not in the weight (p=0.599) and length (p=0.442) of lungs. Furthermore, the Spearman correlation test resulted in a strong correlation between parasitemia and the weight (p=0.000), length (p=0.001), and width (p=0.017) of lungs (Table 1).

DISCUSSION

In this study, based on the physical examination of mice during sacrification, only 3 out of 8 mice developed MA-ARDS. The small number of mice that developed MA-ARDS related to the mouse strain and the strain of parasite used in this experiment. This disease is often associated with cerebral malaria (CM), acute renal failure, and high parasitemia (Gachot et al., 1995; Jindal et al., 2002). Malaria-associated pathogenesis is considered multi-factorial, with both host and *Plasmodium* factors playing critical roles (Epiphanio et al., 2010). Experimental MA-ARDS in *P. berghei* infection have been reported in different strains of mouse and parasite because the development of MA-ARDS in mice was highly dependent on the strain of mice and parasite. When C57BL/6 and BALB/c strains of mice were infected with *P. berghei* NK65-E strain of parasite, only male and female C57BL/6 mice developed MA-ARDS, but not BALB/c mice. Furthermore, when the DBA/2 strain of mice was infected with *P. berghei* ANKA strain, only a lower degree of lung pathology as well as BALB/c mice (Vandermosten et al., 2018).

ARDS is one of severe clinical presentation of malaria infection along with acute lung injury (ALI), cerebral malaria (CM), pregnancy-associated malaria (PAM), and severe anemia (SA). Malaria-associated ALI and ARDS are both lung disorders with similar features as occurred in *P. berghei* ANKA-infected DBA mice. Vascular endothelial growth factor (*VEGF*) is a critical host factor for the onset of malaria-associated ALI. In those mice that developed ALI, VEGF levels increased significantly by day 7 post-infection, but not in BALB/c mice infected with *P. berghei* ANKA because these mice did not develop ALI (Epiphanio et al., 2010).

The MA-ARDS-developed mice found in this study were characterized by the appearance of pleural effusion in the mouse chest cavity and the greyish-brown of lung color. The greyish-brown color of the lungs is caused by bleeding and the increased hemozoin formation (Deroost et al., 2013). Hemozoin (malaria pigment) is a disposal product formed from the digestion of red blood cells by malaria parasites (Soniran, Idowu, Ajayi, & Olubi, 2012). Hemozoin and hemozoin-containing parasites are associated with MA-ARDS and induce pulmonary inflammation (Deroost et al., 2013). Hemozoin is deposited as a brownish granule and caused blockages of small blood vessels in the liver, kidney, spleen, lungs, brain, and heart (Soniran et al., 2012; Franke-Fayard et al., 2010; Deroost et al., 2013; Van den Steen et al., 2013)

Parasitemia in the MA-ARDS group of mice (31.03%) was significantly different from that in the non-MA-ARDS group (12.51%). The MA-ARDS is associated with high parasitemia (Moura et al., 2017). The increase of parasitemia is accompanied by the increase of hemozoin released by schizont-infected erythrocytes when ruptured, therefore as explained above,

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that disposition of hemozoin in various organs causing weight gain and discoloration of the organ.

As found in this experiment, the weight, length, and width of lungs correlated with parasitemia. The disposition of hemozoin and hemorrhages increased lung weights and massive edema, and the hemozoin concentration in the lungs was highly correlated with lung weight and the presence of alveolar edema (Deroost et al., 2013). The lung edema in ARDS is non-cardiogenic pulmonary edema (NCPE), ultimately resulting from capillary permeability secondary to cellular damage, inflammatory cascades, and overinflation by mechanical ventilation resulting in endothelial permeability (Gonzales et al., 2015). The increased lung weight is also due to fluid accumulation causes alveolar collapse, especially in the dependent areas, for example, in the dorsal basal areas of the lungs (Regaller & Richter, 2010). In this study, the higher the parasitemia, the higher the lungs' weight, length, and width. However, a high degree of parasitemia cannot be a reference for MA-ARDS but is characterized by the presence of pleural effusion in the chest cavity, increased lung size, and greyish-brown in lung color.

The limitation of this study was the difficulty of obtaining mice that developed MA-ARDS because the strain of mouse (BALB/c) and parasites (ANKA) used in this experiment were resistant to the experimental cerebral malaria which related to MA-ARDS (Epiphanio *et al.,* 2010), therefore developed a lower degree of lung pathology (Vandermosten et al., 2018).

CONCLUSION

The MA-ARDS in this study pathologically was low; however, parasitemia and lung size between MA-ARDS and non-MA-ARDS were significantly different. High parasitemia correlated with weight, length, and width of the lung in MA-ARDS in BALB/c mice infected with *P. berghei* ANKA.

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Research Article

Compliance in taking medication for hypertension patients listed at Healthy Indonesia Program with a Family Approach

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ABSTRACT

Compliance is the main factor in determining the success of treatment of hypertension and is needed for controlling the prevention of complications so that it is included in one of the Healthy Indonesia Program with a Family Approach (PIS-PK/*Program Indonesia Sehat dengan Pendekatan Keluarga*) indicators. This research aims to determine the relationship between education level, economic status, and knowledge level with compliance in taking medication. This research was observational analytic with a cross-sectional approach. The respondents in this study were hypertension patients listed on PIS-PK in the Mijen District for the period January-August 2020, which included the inclusion and exclusion criteria of 45 respondents. Primary data were obtained using MMAS-8, HK-LS, and a hypertension management knowledge questionnaire. Technique sampling was used consecutively. Data analysis used the Spearman rank correlation test. In this research can be concluded education level (p= 0.025) with relation coefficient (r=0.334) and economic status (p=0.000) with relation coefficient (r=0.550), level of knowledge about hypertension (p=0.000) with relation coefficient (r = 0.545) and knowledge about hypertension management (p=0.005) with relation coefficient (r = 0.413). The higher level of education, the economic status, the level of knowledge its makes higher the compliance in taking medication for hypertension patients listed on the Healthy Indonesia Program with a Family Approach in the Mijen District.

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INTRODUCTION

Hypertension is an increase in systolic blood pressure 140 mmHg and diastolic blood pressure 90 mmHg in two measurements with an interval of five minutes in a state of sufficient rest/quiet (Unger T, Borghi C, Charchar F, 2020). Data and Information Center of the Indonesian Ministry of Health in 2019 presented data on Basic Health Research (Riskesdas) in 2018. The prevalence of hypertension in the population >18 years based on national measurements was 34.11%. According to these data in terms of medication adherence, as many as 54% of hypertension patients regularly take medication, 32.27% of hypertensive patients do not routinely take medication, and 13.33% of hypertensive patients do not take medication at all (Kementrian Kesehatan RI., 2018).

Compliance in taking medication for hypertension patients is included in one of the indicators in the Healthy Indonesia Program with a Family Approach (PIS-PIK/ *Program Indonesia Sehat dengan Pendekatan Keluarga*). Healthy Family Index Data in 2019 nationally hypertension is 24.36% (Kementrian Kesehatan RI., 2020). In comparison, the Healthy Family Index data for hypertension in Central Java province is 21.04%. In the city of Semarang, hypertension patients who take medication regularly are only 30.17%. The lowest is in the Mijen sub-district of 15.01% with a healthy family index of only 0.35, meaning that the family is not healthy (Permenkes No 39 Tahun 2016 Tentang Pedoman Penyelenggaraan Program Indonesia Sehat Dengan Pendekatan Keluarga., 2016). There are two health centers in Mijen District, namely Karangmalang Health Center and Mijen Health Center. The lowest Healthy Family Index Karangmalang health center is Wonoplumbon village 9.68%. Meanwhile, the lowest Healthy Family Index Mijen Public Health Center was Bubakan sub-district 13.39% (Kementrian Kesehatan RI., 2019).

Behavior can affect compliance. In Lawrence Green's Theory, behavior is influenced by predisposing factors, supporting factors, and reinforcing elements (Notoatmodjo, 2014). Knowledge is a predisposing factor that facilitates the occurrence of a behavior. If a person's knowledge is good, they will obey in taking treatment because that person desires to recover so that it encourages the formation of compliance behavior (Darker CD, 2011).

Knowledge in particular about hypertension and its management will significantly affect compliance in taking medication. Reinforced by previous research, there is a significant relationship between patients' knowledge of hypertension and adherence to taking medication (Aldano A. Limbong, Adisti Rumayar, 2018). Based on this concept, knowledge may be related to compliance in taking medication in patients with hypertension (Budi et al., 2016).

Compliance in taking medication in patients with hypertension is also influenced by several other factors such as the level of knowledge, motivation, support from health workers, family support, the influence of the number of drugs consumed, access to health services, employment status, education level, length of suffering, participation in health insurance, and economy (Puspita, 2016) (Pujiyanto, 2018).

In several previous studies, it was found that education was related to compliance in taking medication for hypertension patients. Still, some studies stated that education was not associated with compliance in taking medication for hypertension patients. The minimum number of studies that discuss the factors that influence adherence to taking hypertension medication makes researchers interested in conducting this study.

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METHODS

This study was approved by the Medical Faculty University Muhammadiyah Semarang ethical commission with the number 028/EC/FK/2021. This study used an observational analytic method with a cross-sectional approach. The study was conducted in the Mijen Public Health Center and Karangmalang Health Center in Mijen District from January to February 2021. 45 respondents met the inclusion and exclusion criteria using a consecutive sampling technique.

Inclusion criteria were all hypertensive patients that were listed at PIS-PK and treated for at least 1 month in the Mijen Health Center and Karangmalang Health Center, more than18 years old, willing to become research respondents. Meanwhile, the exclusion criteria were hypertensive patients with mental, cognitive, and psychiatric disorders, hypertension patients with complications such as coronary heart disease, stroke, heart failure, and kidney disease.

The study used primary data from MMAS-8 (Modifed Morisky Adherence Scale) questionnaire (Morisky DE, Ang A, Krousel WM, 2018) (Harijanto W, Rudijanto A, 2015), Hypertension Knowledge Level Scale (HK-LS), hypertension management knowledge questionnaire that had passed the validity and reliability tests and direct interviews as well as secondary data obtained from the annual report of the *puskesmas* containing PIS-PK data for hypertension patients and medical record. The Spearman Rank correlation test analyzed data; p-value ≤ 0.05 means a relationship between the independent and dependent variables. (Dahlan, 2014) Interpretation of relationship level using correlation interpretation guidelines as follows:

1) 0.00 – 0.199 : very low relationship
2) 0.20 – 0.399 : low relationship
3) 0.40 – 0.599 : moderate relationship
4) 0.60 – 0.799 : strong relationship
5) 0.80 – 1,000 : very strong relationship

RESULTS

Based on the table 1 above shows that the majority of the respondents are in the 46-55 year old group (31.1%), female respondents (77.8%), respondents with basic education level as many (80.0%), respondents with low economic (77.8%), respondents who know about low hypertension (75%), respondents who know good hypertension management (65.9%), and majority respondents have low compliance in taking medication levels (75%).

Based on table 2 above shows low compliance to the question "*Have you ever stopped taking medication or reduced the dose without telling your doctor because of the unpleasant effects of taking high blood pressure medication*?" by 22.2%. And high adherence to the question "*Take medicine every day is really uncomfortable for some people, have you ever felt disturbed while taking your high blood pressure medication?*" by 75.6%.

Based on table 3, the results of the analysis of the correlation between education level and compliance in taking medication obtained a correlation coefficient of +0.334 which means that there is a low relationship with a positive distribution direction, namely increasing the level of education, the level of compliance in taking medication will also increase. The Spearman rank correlation test results in a p-value of 0.025 which means that there is a significant relationship between education level and compliance in taking medication. The analysis of the relationship between economic status and compliance in taking medication obtained a correlation coefficient of +0.550 which means that there is a moderate relationship with a positive distribution direction, namely increasing economic status, increasing the level of compliance taking medication. The Spearman rank correlation test results in the value of p = 0.000, which means a significant relationship between education level and compliance in taking medication.

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Table 1. Univariate analysis based on age, gender, education level, level of knowledge about hypertension and hypertension management, economic status, and compliance in taking medication.

Variable	f (n=45)	%
Age		
17-25	3	6.7
26-35	3	6.7
36-45	4	8.9
46-55	14	31.1
56-65	14	31.1
>65	7	15.6
Gender		
Male	10	22.2
Female	35	77.8
Education Level		
Basic	36	80.0
Middle	7	15
High	2	80,0
Level of knowledge about hypertension		
High	5	11.1
Middle	7	15.6
Low	33	73.3
Level of knowledge about hypertension management		
High	29	64.5
Low	16	35.5
Economic Status		
High	35	77.8
Low	10	22.2
Compliance in taking medication		
Low	36	80.0
Middle	7	15.6
High	2	4.4

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Table 2. Compliance Assessment Based on MMAS-8

Description	Yes (%)	No (%)	Total (%)
Do you sometimes forget to take medication?	64.4	35.6	100.0
Within 2 weeks. are there days that you dont take medication not because you forgot?	53.3	46.7	100.0
Have you ever stopped taking medication or reduced the dose without telling the doctor because you felt bad effects when taking medication?	77.8	22.2	100.0
When you travel or leave the house. do you sometimes forget to bring your medication?	28.9	71.1	100.0
Did you not take medication yesterday?	55.6	44.4	100.0
When you feel your blood pressure is under control. do you sometimes stop taking medication?	66.7	33.3	100.0
Taking medicine every day is really uncomfortable for some people. have you ever felt disturbed when taking your medication?	24.4	75.6	100.0
How often do you have trouble remembering to take medication?	51.1	48.9	100.0

Table 3. Analysis Result Rank Spearman Test

Variable	p	r
Economis status	0.000	0.550
Education Level	0.025	0.334
Level of knowledge about hypertension	0.000	0.545
Level of knowledge about hypertension management	0.005	0.413

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The results of the analysis of the correlation between the level of knowledge about hypertension and compliance in taking medication obtained a correlation coefficient of +0.545 which means that there is a low relationship with a positive distribution direction, namely increasing the level of knowledge about hypertension, the level of compliance in taking medication will also increase. The Spearman rank correlation test results in the value of p = 0.000, which means that there is a significant relationship between the level of knowledge about hypertension and compliance in taking medication. The results of the analysis of the correlation between the level of knowledge about the management of hypertension and compliance to taking medication obtained a correlation coefficient of +0.413 which means that there is a moderate relationship with a positive distribution direction, namely increasing economic status, increasing the level of compliance in taking medication. The Spearman rank correlation test results in a p-value of 0.005 which mean that there is a significant relationship between the level of knowledge about hypertension management and compliance in taking medication.

DISCUSSION

Based on result, respondents who have compliance in taking medication.get a low score due to several points, namely, firstly, intentionally stopping taking medication without the doctor's knowledge, secondly stopping taking medication because they feel that their blood pressure is under control, thirdly the frequency of forgetting to take medicine, fourthly schedule. The previous day, the fifth within 2 weeks did not take medicine, the six patients had difficulty remembering to take the medication, the seventh was the availability of treatment while traveling, and the last one was due to the inconvenience of taking medicine every day.

Educational level was significantly related to compliance in taking medication in hypertension patients in Mijen District. According to the interview, respondents with a basic education tend to have low compliance scores because they think they take medication only when complaints of hypertension arise and when complaints subside, they tend to stop taking medication. Respondents with basic education levels also tend to often forget to take their medicine. Respondents with a middle education level tend to have moderate compliance scores because they feel disturbed by taking medication every day and think that taking medication every day will negatively impact the kidneys. Respondents with high education tend to have high compliance scores because they think that hypertension requires regularity in taking medication so that blood pressure is controlled to avoid complications. The results of this study are in sync with previous research; there is a significant relationship between the level of education and compliance in taking medication in patients with hypertension at the Kajen Regional General Hospital, Pekalongan Regency (Ahda, 2016). Education can influence health behavior because education makes a person more able to absorb and get news from health workers. The mindset is more developed, logical and considers various considerations to maintain or overcome health problems (Notoatmodjo, 2011). The increase in education history will increase compliance to taking medication (Notoatmodjo, 2010).

According to this study, it was found that the economic status of the respondents was significantly affiliated with compliance in taking medication in hypertension patients in Mijen District. Based on the interviews, respondents with low economic status have low compliance scores because they are less able to meet their daily needs, so they choose not to visit the *puskesmas* to take medicine regularly. Hypertension patients get free medicine

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through programs at the Puskesmas, but they have difficulty taking medication because of the high transportation costs to reach the *puskesmas*. Respondents with high economic status have moderate to high compliance scores because they can meet their daily needs. So respondents with the high financial situation do not take medication at the health center. They will check with private practice doctors or buy drugs at pharmacies independently. The results of this study are in sync with previous research, namely, the level of income is one of the socioeconomic factors affecting hypertension patients in compliance to taking medication (Pujiyanto, 2018) (Rasajati QP, Raharjo BR, 2015).

Economic status can affect health behavior because income affects health consumers and health services to control problems related to health (Notoatmodjo, 2011). As financial status increases, compliance to medication also increases (Notoatmodjo, 2010).

This study found that knowledge about hypertension and its management had a significant relationship with compliance in taking medication. Based on the results of the answers to the questionnaire, most respondents did not know about medical treatment and complications related to hypertension. The majority of respondents do not take medicine every day but only take medicine when they feel sick. The majority do not know that hypertension will cause advanced diseases such as visual disturbances and kidney and heart disease if not treated immediately.

Based on the results of this study, the majority of respondents did not routinely check their blood pressure at the *puskesmas*; respondents usually visit the *puskesmas* when they feel unbearable symptoms. If the patient does not feel the symptoms of hypertension such as dizziness and the neck feels heavy, they think their blood pressure has returned to normal, and then they do not take medication. So that the lack of knowledge about hypertension and its management causes respondents not to have the self-awareness to change lifestyle behavior towards a healthier direction and do not understand the importance of taking medication every day. The theory states that a fundamental domain in shaping one's actions is knowledge. If it is based on the understanding of the behavior, it will be lasting (Notoatmodjo, 2014). In line with previous research, knowledge in patients with high blood pressure can affect regularity in taking medication (Ikhwan M, Livana PH, 2017) (Haldi T, Pristianty L, 2021).

The benefit of this research is that it can add reference material for improving service policies in Healthy Indonesia Program with a Family Approach. The limitation of this research is that it used a cross-sectional method, so that it is difficult to assess cause and effect because data collection is carried out at the same time.

CONCLUSION

According to the analysis and discussion results, it can be concluded that the increase in education level, level of knowledge about hypertension and its management, and economic status will increase the level of compliance to taking medication.

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Research Article

Analysis of the relationship between using personal protective equipment (PPE) masks on the incidence of respiratory symptoms disorders of online motorcycle taxi drivers in Malang

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ABSTRACT

Health problems that are often encountered due to work are respiratory disorders that cause premature death every year. Exposure to pollution is harmful to health, and chronic exposure causes lung cancer and COPD. The use of masks is an alternative in reducing exposure to pollution. This study aimed to determine the relationship between the habit of wearing masks on the incidence of respiratory symptoms disorder of online motorcycle taxi drivers in Malang. This study was an analytic observation with a cross-sectional design. Samples were determined using the comparative bivariate analytical sample formula. The data were analyzed using a univariate test and bivariate analysis with a chi-square test. This study showed a significant relationship between the habit of wearing a mask with p score = 0.015 ($p<0,05$), changing time with p score = 0.004 ($p<0,05$), and the type of mask on respiratory symptoms disorders with p score = 0.006 ($p<0,05$). The results obtained regarding the description of the habit of using masks, the results of the method of using masks were mainly in the good category. In conclusion, there is a significant relationship between the habit of wearing masks and the incidence of respiratory symptoms disorders among online motorcycle taxi drivers in Malang.

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INTRODUCTION

Globally, there are an estimated 2.3 million work-related deaths each year, with 86.9% due to work-related illnesses. In the UK, deaths from exposure to chemicals, dust, and fibers in the workplace have increased over the last 40 years, with currently around 13,000 premature deaths annually from lung disease and occupational cancer (Dimakakou et al., 2018). Exposure to air pollution is of particular concern because 91% of the world's population lives in areas with poor air quality and exceeding the World Health Organization guidelines (Zhong et al., 2021).

In urban areas, motorized vehicles are responsible for air pollution caused by their exhaust emissions (Lawin, Fanou, Hinson, et al., 2018). Bus, car, and motorcycle drivers in urban areas are at risk of being exposed to air pollution while working, and the vehicles they drive are a source of air pollution for other communities and other drivers, which will be harmful to health, resulting in respiratory morbidity, decreased lung function, and even cause heart problems and on chronic exposure can cause lung cancer and COPD (Damayanti et al., 2019; Lawin, Fanou, Kpangon, et al., 2018; Sasikumar et al., 2020)

The use of masks is an alternative in reducing pollution exposure, which is very practical, inexpensive, and can protect oneself from the transmission of acute respiratory infections (Hansstein & Echegaray, 2018). In general, masks are protective equipment with the primary function of reducing the transmission of particles or droplets and other infectious agents (Fischer et al., 2020). The mask filters particles when the air is inhaled, and then there is capture and deposition of particles by the filter fiber on the mask. The use of a mask can prevent the possibility of respiratory system disorders due to exposure to air with high dust levels (Muthia & Hendrawan, 2017).

Based on those facts and problems, the authors want to conduct a study that aims to determine the relationship between personal protective equipment masks on respiratory symptoms disorders of online motorcycle taxis drivers In Malang.

METHODS

This research has earned ethical approval from the ethics committee of University of Muhammadiyah Malang (Certificate number: E.5.a/057/KEPK-UMM/VI/2021). This type of research is analytic observation with a cross-sectional design to determine the relationship between wearing PPE masks and the incidence of respiratory symptoms disorders of online motorcycle taxis drivers in Malang. The population in this study were online motorcycle taxis drivers in Malang.

The inclusion criteria were; respondents agreed to the informed consent to participate in the study, work at least five days a week, use a mask while working, and work for at least one year. The exclusion criteria was smoked. While the drop out criteria was unable to complete the questionnaire. The sample in this study was the part of the population used as research subjects who meet the inclusion criteria.

This study determined the sampling formula for calculating the relative bivariate analytical sample size (M. Sopiyudin Dahlan, 2020). The sampling technique that will be used in this study is purposive sampling. The independent variable in this study was the habit of using PPE masks for online motorcycle taxis drivers in Malang. The dependent variable was the incidence of respiratory symptoms disorders of online motorcycle taxis drivers in Malang. The research sample was 108 online motorcycle taxis drivers in Malang. Questionnaires were distributed to online motorcycle taxis drivers to determine the relationship between wearing PPE masks and the incidence of respiratory

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symptoms disorders among online motorcycle taxis drivers in Malang. The technical analysis used in this study was SPSS 24 version. The univariate statistical analysis and bivariate analysis with chi-square test were used. The result would be significant if the p-value were <0.05.

RESULTS

The data was obtained based on the respondents' answers which aimed to determine the habit of using PPE masks on the incidence of respiratory symptoms in online motorcycle taxi drivers in Malang City. This study used a questionnaire to assess the relationship between using PPE masks and the incidence of respiratory symptoms experienced by online motorcycle taxi drivers. There were no respondents who dropped out during the research process. Then it was processed according to the purpose of the study to determine the relationship between the habit of using PPE masks on the incidence of respiratory symptoms in online motorcycle taxi drivers in Malang.

Table 1. Distribution of the Number of Types of Masks

Type of Mask	Amount	Percentage (%)
Medical/Surgical Mask	17	15.7
KN 95 mask	0	0
Non-Medical/Fabric Mask	91	84.3
Total	108	100

Table 2. Distribution of Time for Replacement of Used PPE Masks

Mask change time	Amount	Percentage (%)
<4 hours	5	4.6
<12 hours	61	56.5
<24 hours	27	25
>24 hours	15	13.9
Total	108	100

Table 3. Distribution of the Number of Habits on How to Use PPE Masks

The habit of how to use PPE mask	Amount	Percentage (%)
Good	64	59.3
Quite good	24	22.2
Not good	20	18.5
Total	108	100

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Table 4. Distribution of Number of Respiratory Symptoms

Respiratory symptoms	Amount	Percentage (%)
Cough	46	42.6
phlegm	43	39.8
Shortness of breath	6	5.6
Wheezing	10	9.3
Chest feels heavy	21	19.4
Cold	69	63.9
Sore throat	19	17.6

Table 5. The relationship between the type of mask, replacement time, and the habit of using PPE masks and the incidence of respiratory symptoms

Information	*Chi-Square* (χ^2) test	P value
The relationship between the type of mask and symptoms of respiratory disorders	7.598	0.006
The relationship between the habit of wearing a mask with symptoms of respiratory disorders	8.360	0.015
The relationship between the habit of changing masks with symptoms of respiratory disorders	13.108	0.004

Based on table 1, data was obtained from 108 online motorcycle taxis drivers in Malang who became respondents. Most types of masks were non-medical/fabric masks with a percentage of 84.3%, medical/surgical masks by 15.7%, and KN 95 masks by 0%.

Based on table 2, data shows that of the 108 online motorcycle taxis drivers in Malang who became respondents, the group with the most mask replacement time was <12 hours with a percentage of 56.5%, <24 hours by 25%, >24 hours 13.9% and <4 hours by 4.6%.

Based on table 3, data was obtained from the 108 online motorcycle taxis drivers in the city of Malang who were respondents, the most groups of how to use masks, were good with a percentage of 59.3%, quite good at 22.2%, and not good at 18.5%. Classified to be good if the score was in the range of 75-100%, quite good 60-74%, and not good <60%.

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Based on table 4, data was obtained that from 108 online motorcycle taxi drivers in the city of Malang who became respondents, the most respiratory symptoms that occurred were colds with a percentage of 63.9%, coughing 42.56%, phlegm 39.8%, chest feels heavy by 19.4%, sore throat by 17.6%, wheezing by 9.3%, and shortness of breath by 5.6%.

In order to find out whether there is a relationship between the type of mask, the habit of wearing a mask, and the time of changing the mask with respiratory symptoms, it is necessary to form cross tabs that can describe the distribution of data in more detail, as presented in the following table.

Based on the test results in table 5, the chi-square value to determine the relationship between the type of mask and respiratory symptoms disorders, which is 7.598, with a significance value (p) of 0.006 ($p<0.05$), so it can be concluded that between the types of masks and symptoms respiratory disorders have a significant relationship. For the results of testing the relationship between mask replacement time and symptoms of respiratory diseases, namely 13.108, with a significance value (p) of 0.000 ($p<0.05$), so it can be concluded that the time of mask replacement with respiratory symptoms disorders has a significant relationship. For the results of testing the relationship between the habit of wearing a mask with symptoms of respiratory symptoms disorders, which is 8.360, with a significance value (p) of 0.015 ($p<0.05$), so it can be concluded that between the habit of wearing a mask with symptoms of respiratory disorders has a significant relationship.

DISCUSSION

Health problems that are often encountered due to work are respiratory disorders that cause premature death every year. Exposure to pollution is harmful to health, and chronic exposure causes lung cancer and COPD. The use of masks is an alternative in reducing exposure to pollution. This study aimed to determine the relationship between the use of personal protective equipment masks on respiratory symptoms disorders of online motorcycle taxis driver In Malang.

From the analysis result, we can conclude that the type of mask with respiratory symptoms disorders has a significant relationship. According to the International labor organization (2020), the type of mask also affected the incident because the cloth mask itself is not standardized and is not intended to be used to protect oneself from viruses. According to research conducted by (MacIntyre et al., 2015), the use of cloth masks is more at risk of developing respiratory infections than medical masks. Cloth masks perform poorly for motor vehicle combustion particles, with the filtration efficiency of cloth masks for particles emitted from motor vehicle combustion ranging from 15% to 57% for total particle concentration and 13% to 40% for total particle mass (Shakya et al., 2017). Cloth masks lack a protective function against aerosols or airborne particles with filtration effectiveness of three microns (Hapsari & Munawi, 2021).

Medical masks efficiently filter bacteria up to 98% with single-use surgical masks that can protect against airborne particles, droplets, liquids, viruses, or bacteria (Kemenkes RI, 2020; Theopilus et al., 2020). Medical masks have been standardized internationally and nationally to ensure their performance (Zhong et al., 2021). Medical masks effectively perform well for particulate combustion of motor vehicle materials with 78-94% (Shakya et al., 2017).

From the analysis result, we can conclude that the time of changing masks with respiratory symptoms disorders has a significant relationship. This can be happen because the filtration efficiency of cloth masks itself has

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a duration of use for 4-5 hours a day, while medical/surgical masks have a duration of use of 6 hours and have an efficiency in filtering bacteria up to 98% with single use but can experience a decrease in filtration efficiency. After 6 hours (Chughtai et al., 2019; Kobayashi et al., 2020) and according to Dwirusman, (2020), medical masks can protect against bacteria for at least 4 hours. After using it for more than 4 hours, it will increase the occurrence of contamination on the mask due to decreased filtration power (Barbosa & Graziano, 2006).

From the analysis result, we can conclude that the habit of wearing a mask with respiratory symptoms disorders has a significant relationship. According to research conducted by Brooks & Butler (2021), People who are not regularly/disciplined in using masks experience more respiratory problems than people who constantly use PPE with a breathing mask when working. The use of PPE masks must meet requirements such as being comfortable when worn, not interfering with the implementation of work, and providing effective protection against the kinds of hazards faced (Muhith, 2018). The habit of using a good mask tends to prevent the occurrence of respiratory symptoms in the wearer.

The protection from respiratory symptoms can happen because of several reasons. First, drivers wore a mask correctly by covering the mouth and nose when using a mask. So that dirt can be filtered and does not enter the respiratory tract (Machida et al., 2020; Muthia & Hendrawan, 2017). Second, drivers wore more than one layer of the mask, which increased filtering efficiency (WHO, 2021). The more layers of fabric and the density of the cloth weave, the filtering efficiency increases by more than 80% for small particles and more than 90% for large particles (Hapsari & Munawi, 2021). Third, drivers remove the mask from the back and not touch the mask when used. It can prevent mask contamination (Machida et al., 2020). Fourth, drivers replace the mask when the mask is damp because there will be a decrease in mask performance if it becomes damp (Dwirusman, 2020; Machida et al., 2020). Fifth, drivers wash the cloth mask with soap before using it again. The use of PPE masks themselves must be appropriate both in terms of type, method of use, method of removal, and method of disposal or washing of masks, where the use of PPE masks is an aspect of prevention and self-protection from diseases including respiratory diseases (Kemenkes, 2020).

The limitations of this study were the absence of supporting tools other than a questionnaire to assess the status of the respondent's respiratory function and the lack of measurement of exhaust gas emission tests in Malang. So the recommendations for further study are to use supporting tools like spirometry, the medical record of online motorcycle taxis drivers must be known and excluded the respondents who had a history of chronic respiratory disease.

CONCLUSION

Regarding the description of the habit of using masks for online motorcycle taxis drivers in the city of Malang, most groups of how to use masks were in a good category. Based on the result, there is a significant relationship between the habit of wearing a mask, the habit of changing masks, and the type of mask on the incidence of respiratory symptoms among online motorcycle taxi drivers in Malang City.

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Research Article

The effect of ginger (*Zingiber officinale*) extract on the neutrophil level and CAT (COPD Assessment Test) scores in workers with COPD due to dust exposure

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that does not fully return to normal and is associated with the increased inflammatory response in the airways due to exposure to noxious particles or gases. Workers are susceptible to exposure to steam, dust, gases, and fumes in the work environment. Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress to reduce the inflammatory response. Ginger contains various active ingredients that act as antioxidants. The research design is a quasi-experimental study with a pre-test and post-test approach. The research subjects were 30 subjects workers diagnosed with COPD. Subjects were divided into two groups: the control group was given standard therapy, the treatment group was given standard therapy and ginger extract. The treatment was given for one month, then the neutrophil and the COPD Assessment Test (CAT) scores were checked. The data were analyzed with an unpaired difference test. The treatment group (-5.67 +2.32) experienced more CAT decline than the control group (-0.73 +1.28) and showed a significant difference; this was evidenced in the unpaired difference test on the post-pre difference value (p = <0.001). The treatment group (-4.93 +4.43) experienced more neutrophil decline than the control group (0.27 +1.10) and showed a significant difference; this was evidenced in the unpaired difference test on the post-pre difference value (p = < 0.001). Administration of ginger extract can reduce neutrophil levels and CAT scores in COPD workers due to dust exposure.

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INTRODUCTION

A number of respiratory illnesses in workers have been linked to exposure to inhaled dust. Occupations with exposure to high amounts of dust such as wood mills, cigarettes, and rice mills are associated with an increased prevalence of respiratory symptoms such as shortness of breath, coughing, irritation of the eyes and nose, and the risk of developing chronic obstructive pulmonary disease (COPD) (Asri et al., 2020; Löfstedt et al., 2017). This progressive disease is characterized by airflow limitation that does not fully return to normal and is associated with increased inflammatory response in the airways caused by exposure to harmful gases or particles. A study conducted in Spain found that COPD prevalence was 9% in men aged over 40 years and 20% of those over 65 years (Aisanov et al., 2019). Overall, 10-15% of COPD sufferers are associated with occupational exposure (Fishwick et al., 2015). The incidence of COPD is relatively high among workers due to exposure to steam, dust, gas, and smoke in the work environment. This makes COPD one of the most challenging diseases in the future (Molen et al., 2018; Perhimpunan Dokter Paru Indonesia, 2016).

Establishing a COPD diagnosis should be considered in patients with symptoms of chronic cough, shortness of breath, and sputum production with a history of exposure to motor vehicle fumes, cigarette smoke, household smoke, burning smoke, and chemical fumes or dust in the workplace. In COPD, the abnormal inflammatory response that occurs in COPD involves neutrophils along with other inflammatory cells, including macrophages and CD81 T lymphocytes, which play a role in producing structural changes in the airways (Stockley, 1999).

The COPD Assessment Test (CAT) score is a method in the form of a validated, easy-to-implement questionnaire consisting of eight statement items to find out about health status in COPD (Report, 2009; Stockley, 1999). The CAT score also serves as a component for clinical assessment, helping to monitor the effects of COPD such as rehabilitation programs or improvement of exacerbations so that the therapy given can be optimal (Feliz-Rodriguez et al., 2013; Roca et al., 2013).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed international standard treatment guidelines for stable and exacerbating COPD patients. These guidelines have been through extensive clinical trials and evidence. Giving standard therapy did not stop the progression of the disease. Therefore, the provision of additional therapy is needed to further slow down, stop, or replace the damage that has occurred. The basis for giving this additional therapy still refers to the pathogenesis of COPD in the form of oxidative stress, inflammation, protease-antiprotease imbalance, and apoptosis (Global Initiative for Chronic Obstructive Lung Disease, 2014; Roca et al., 2013).

Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response. Ginger is a herbal medicine that has a high antioxidant effect. Ginger extract is obtained easily, and the price is relatively low because there are many ginger extract products on the market. Ginger contains many components of active ingredients, such as phenolics and terpenes. Ginger acts as an antioxidant by inhibiting the production of reactive species antigens and lipid peroxidase (Hansel & Barnes, 2009; Mao et al., 2019).

The purpose of this study was to analyze the effect of giving ginger extract on respondents suffering from COPD due to dust through the assessment of neutrophils in the blood and CAT

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scores. The results of this study are expected to be helpful in the field of occupational health. Regular administration of ginger is thought to prevent and reduce the severity of COPD due to dust exposure.

METHODS

This was a quasi-experimental study, with pre-test and post-test control groups design and using consecutive sampling. The study was conducted at the Muhammadiyah Hospital in Central Java, sampling from June – August 2021.

The subjects are workers with COPD due to dust exposure who are routinely controlled at the Pulmonary Polyclinic at the Muhammadiyah Hospital in Central Java. The inclusion criteria were patients in stable condition, aged more than 40 years, having a work history of more than 15 years, not an active smoker, and willing to participate in the study. The exclusion criteria were patients with chronic renal failure, patients with diarrhea, patients who received other herbs during the study, and the discontinuous criteria were patients who withdrew from the study and patients who experienced severe side effects during treatment.

The sample size was determined based on unpaired numerical analysis, with a total sample size of 30 people. This study used a sample size of 30 subjects consisting of 15 subjects in the treatment group and 15 subjects in the control group.

The treatment group received standard COPD therapy plus ginger extract, while the control group received standard COPD therapy. Treatment using ginger extract capsules from Borobudur herbal products, and this research has received ethical approval with the issuance of ethical clearance no: 067/EC/FK/2021 issued by the Health Research Ethics Committee, Faculty of Medicine, Muhammadiyah University, Semarang.

Data analysis was performed using SPSS 21. Comparison between the independent and dependent variables using a different test. The difference test is the result of a test to see the difference between two samples. Measurement of neutrophil samples using an automatic hematology analyzer with whole blood sampling and measurement of CAT score using a standardized CAT questionnaire. This study uses paired samples with paired t-test. CAT score difference before and after administration of ginger extract in COPD patients who received ginger extract compared to the control group will be analyzed using an unpaired t-test. The effect of giving ginger extract on CAT score between pre and post-treatment was analyzed using a different test technique pre-post treatment (paired t-test).

RESULTS

Characteristics of Research Subjects

The study results obtained the characteristics of the research subjects in the form of age, gender, occupation, length of work, and education. The statistical test used for categorical data is the chi-square test / Fisher exact test, while the statistical test for numerical data is the Mann-Whitney test. Normality test was done by Shapiro Wilk test. The significance value used in this study is = 5%. The results are as seen in Table 1.

Table 1 shows that the results of the statistical test of patient characteristics in the treatment group and control group with a p-value >0.05 (there is no significant difference) are age ($p = 0.383$), occupation ($p = 0.761$), length of work ($p=0.080$), and education ($p=0.519$). In comparison, the gender is $p = 0.0003$ ($p <0.05$), which means there is a significant difference between patients in the treatment and control groups.

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Table 1. Characteristics of Research Subjects

No	Characteristics	Group		Total	p-value
		Treatment	Control		
1	Age (years)	64.00 +12.58	60.27 +10.37	62.13 +11.48	0.383
2	Gender				0.003*
	Male	13 (86.7%)	5 (33.3%)	18 (60.0%)	
	Female	2 (13.3%)	10 (66.7%)	12 (40.0%)	
3	Work				0.761
	Construction Laborers	4 (26.7%)	2 (13.3%)	6 (20.0%)	
	Ricemill worker	4 (26.7%)	6 (40.0%)	10 (33.3%)	
	Stone craftsman	1 (6.7%)	3 (20.0%)	4 (13.3%)	
	DL sweeper	1 (6.7%)	1 (6.7%)	2 (6.7%)	
	Bricklayer	2 (13.3%)	1 (6.7%)	3 (10.0%)	
	Carpenter	3 (20.0%)	2 (13.3%)	5 (16.7%)	
	Length of work	33.87 +9.41	27.67 +6.78	30.77 +8.65	0.080
4	Education				0.519
	Elementary school	8 (53.3%)	5 (33.3%)	13 (43.3%)	
	Junior high school	6 (40.0%)	8 (53.3%)	14 (46.7%)	
	Senior High School	1 (6.7%)	2 (13.3%)	3 (10.0%)	

Information: *[a]Numerical data is normally distributed, independent test t test;*
[b]Nominal categorical data; frequency (%), chi square test/fisher exact test;
[c] Numerical data is not normally distributed or ordinal categorical data, Mann Whitney test;
**significant at =5%*

Table 2. CAT Score Difference Between Control Group and Treatment Group (*Zingiber officinale*)

No	Group	CAT			
		Pre	Post	p	Post – Pre
1	Treatment	30.67 +2.16	25.00 +2.14	<0.001[c]	-5.67 +2.32
2	Control	30.40 +1.30	29.67 +1.11	0.046[d]	-0.73 +1.28
	p	0.305[a]	<0.001[a]		<0.001[b]

Note: *Observation results are described with a mean ± SD,*
***a**: unpaired group difference test did not pass the normality requirement (Mann Whitney);*
***b:** unpaired group difference test passed the normality requirement (independent t-test););*
***c**: test for different groups in pairs passed the normality requirement (pair t-test);*
***d**: The paired difference test did not pass the normality requirement (Wilcoxon rank test).*
Changes are declared significant if the test results in $p < 0.05$.

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Different Test of CAT Pre, Post, and Post-Pre Differences Control Group and Treatment Group (*Zingiber officinale*)

Based on the Shapiro Wilk test, the distribution of data from CAT observations in the unpaired group difference test did not pass the normality requirement; the different test with Mann-Whitney was pre-test and post-test data. In contrast, the data that met the assumption of normality used the independent t-test test, namely the post-pre difference data. The paired difference test of the treatment group passed the normality requirement, the difference test was carried out with the paired t-test, while the control group did not pass the normality requirement. The different test was carried out with the Wilcoxon rank test. The results are shown in Table 2.

Based on Table 2 the treatment and control groups experienced a statistically significant change in the decrease in CAT. The subjects of the *Zingiber officinale* supplementary treatment group experienced a more significant reduction in CAT than the control group and showed statistically significant differences. Thus, the *Zingiber officinale* group was more effective in reducing CAT compared to the control group.

Pre, Post, and Post-Pre Neutrophil Difference Test for Control Group and Treatment Group (*Zingiber officinale*)

Based on the Shapiro Wilk test, the distribution of data from observations of neutrophils in the unpaired group difference test passed the normality requirements, the different test with independent t-test, namely pre-test and post-test data. Meanwhile, data that did not meet the assumption of normality using the Mann Whitney test, namely the post-test difference data. The paired difference test of the treatment and control groups passed the normality requirement. The difference test was carried out with the paired t-test as seen on Table 3.

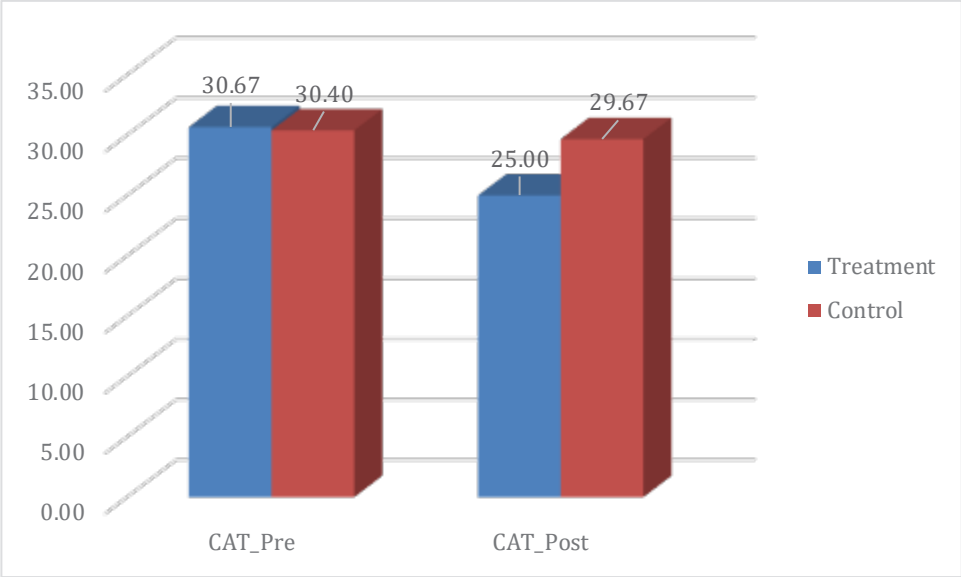

Figure 1. Comparison of CAT Score Results between treatment (*Zingiber officinale*) and control group

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Table 3. Neutrophil Difference Test Between Control and Treatment Group (*Zingiber officinale*)

NO	Group	Neutrophil			
		Pre	Post	p	Post – Pre
1	Treatment	60.80 +6.78	55.87 +6.85	0.001	-4.93 +4.43
2	Control	60.20 +4.28	60.47 +4.41	0.364	0.27 +1.10
	P	0.774[a]	0.037		<0.001[b]

Information: *The results of observations are described with a mean ± SD,*
a: *unpaired group difference test passed the normality requirement (Independent t-test);*
b: *unpaired group difference test did not pass the normality requirement (Mann Whitney);*
c: *test for different groups in pairs passed the normality requirement (pair t-test).*
Changes are declared significant if the test results in p < 0.05, neutrophil in cells/µL

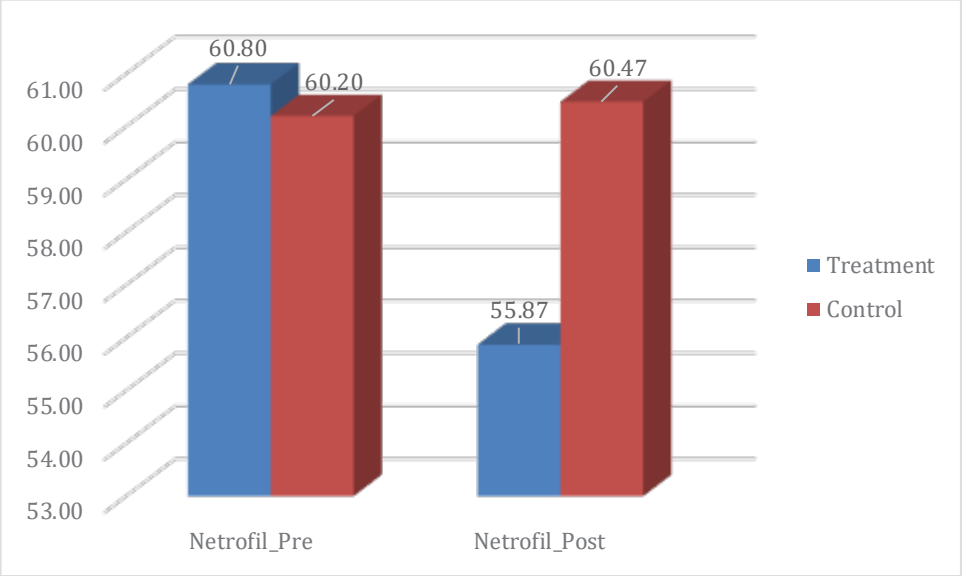

Figure 2. Comparison of Neutrophil Examination Results between treatment groups (*Zingiber officinale*) and control (cells/µL)

Based on the results of Table 3, the treatment group experienced a statistically significant change in neutrophil decline. In contrast, the control group did not experience a significant change in neutrophils. Subject which receive additional *Zingiber officinale* treatment, experienced more neutrophil reduction than the treatment group and showed a statistically significant difference. Thus, the *Zingiber officinale* group was more effective in reducing neutrophil levels than the control group.

DISCUSSION

Lung disease due to oxidative stress occurs due to molecular changes in the complex interactions of multiple genes and oxidants. These changes are due to oxidants' direct or indirect action on target cells. The direct action of oxidants is in the form of peroxidation of cell membrane lipids, proteins, and deoxyribonucleic acid (DNA). The indirect action of oxidants is through protease activation, antiprotease inactivation, transcription of proinflammatory mediators,

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and apoptosis (Barnes PJ, Drazen JM, Rennard S, 2529; Löfstedt et al., 2017; Mao et al., 2019).

Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response. Ginger is a herbal medicine that has a high antioxidant effect. Ginger contains many components of active ingredients, such as phenolics and terpenes. Ginger acts as an antioxidant by inhibiting the production of reactive species antigens and lipid peroxidase (Fishwick et al., 2015; Perhimpunan Dokter Paru Indonesia, 2016).

The COPD Assessment Test (CAT) is a method in the form of a validated, easy-to-apply questionnaire consisting of eight statement items to find out about health status in COPD (Global Initiative for Chronic Obstructive Lung Disease, 2014; Molen et al., 2018). The CAT score can be used for all patients diagnosed with COPD unstable and exacerbating COPD at all degrees of severity (Report, 2009; Stockley, 1999). The results showed that subjects given additional treatment with Zingiber officinale (-5.67 +2.32) experienced more CAT reduction than the control group (-0.73 +1.28) and showed statistically significant differences evidenced in the unpaired difference test. on the value of the post-pre difference (p = <0.001). Thus, the *Zingiber officinale* group was more effective in reducing CAT score compared to the control group.

The active components in ginger induce bronchodilation by modulating intracellular calcium Ca21 in airway smooth muscle. Ginger induce relaxation of human airways rapidly and significantly. The four active components were then tested to relax airway smooth muscle in the guinea pig and human tracheas: [6] -gingerol, [8] -gingerol, and [6] -shogaol induced rapid relaxation of airway smooth muscle (100–300 mM), whereas [10]-gingerol failed to induce relaxation. In human airway smooth muscle cells, exposure to [6]-gingerol, [8]-gingerol, and [6]-shogaol, but not [10]-gingerol (100 mM), blunted the subsequent Ca21 response to bradykinin (10 mM). Another study conducted on rats treated with nebulized [8]-gingerol (100 mM), 15 minutes before the administration of methacholine, significantly reduced airway resistance. These new data suggest that ginger and its isolated active components, [6]-gingerol, [8]-gingerol, and [6]-shogaol, relax airway smooth muscle, and [8]-gingerol attenuates airway hyperresponsiveness, breath, in part by altering Ca21 regulation. This purified active component can provide an alternative to single therapy or combined with primary therapies, including ß2-agonists, in airway disease (Feliz-Rodriguez et al., 2013; Hansel & Barnes, 2009; Perhimpunan Dokter Paru Indonesia, 2016; Roca et al., 2013). Based on the description above, it is known that the active substance in ginger can reduce the production of oxidative stress, suppress the formation of lipid peroxidase and nitric oxide. Inhibition of oxidative stress formation will inhibit the decrease in elastin degradation, thereby inhibiting airway damage. Airflow obstruction in COPD can be identified through the COPD CAT scoring examination. Thus the hypothesis which states that "*There is an effect of giving ginger extract on the CAT score of workers with COPD due to dust exposure*" is proven.

Neutrophils are one of the phagocyte systems in the human body that have the largest component. The role of neutrophils is crucial in terms of the body's defense from foreign dangers ranging from acute to chronic processes. COPD attacks the airways and has such systemic manifestations as elevated C-reactive protein. Activation of peripheral blood neutrophils by cytokines has been shown to occur. This activation is thought to be related to disease severity. Systemic neutrophils in COPD patients enhance extracellular

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chemotaxis and proteolysis (Shetkar & Pyati, 2018).

This study shows that the subjects given additional treatment with *Zingiber officinale* (-4.93 +4.43) experienced more neutrophil reduction compared to the control group (0.27 +1.10) and showed statistically significant differences. This is evidenced in the no different test paired on the post-pre difference value (p= <0.001). Thus, the *Zingiber officinale* group was more effective in reducing neutrophil levels than the control group.

The anti-inflammatory effect of ginger may be related to inhibiting the biosynthesis of prostaglandins and leukotrienes. Several other studies have shown that gingerols actively inhibit arachidonate 5-lipoxygenase, a leukotriene biosynthetic enzyme. The compound [8]-gingerol in ginger has been shown to inhibit the expression of cyclooxygenase-2 (COX-2), which is induced during inflammation to increase the formation of prostaglandins. Some of the anti-inflammatory effects of ginger appear to be related to decreased IκBα degradation and impaired translocation of nuclear factor-κB (NF-κB) p65. The main scientific evidence indicates that ginger and its various components have anti-inflammatory effects both in vitro and ex vivo. However, data supporting ginger as an effective anti-inflammatory agent in humans in vivo is incomplete (Barbu et al., 2011; Cho et al., 2015; Desai et al., 2012; Global Initiative for Chronic Obstructive Lung Disease, 2014; Koh et al., 2009; Mao et al., 2019; Oemiati, 2013; Perhimpunan Dokter Paru Indonesia, 2016). Thus, giving ginger as an antioxidant can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response, which has an impact on decreasing neutrophils.

The limitations of this study are the lack of samples that are treated, and there are still other confounding factors that cause COPD. It is hoped for further research so that the subject is more comprehensive and these confounding factors can be controlled.

CONCLUSION

There is an effect of giving ginger extract on reducing neutrophil levels and CAT scores in COPD workers due to dust exposure. Therefore, the supplementation in the form of ginger can be recommended so that the quality of life of these workers will improve.

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Case Report

Bradycardia, renal failure, shock, and hyperkalemia (BRASH) caused by AV nodal blocker: a case report of a patient with BRASH syndrome resistant to calcium administration

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ABSTRACT

Chronic kidney disease patients commonly present in a clinical setting with hypertension may cause or affect the disease. Carvedilol, a beta-blocker that is routinely used to treat hypertension in chronic kidney disease, was proven to be safer compared to other beta-blockers. However, it may still cause AV nodal block. AV nodal block can cause bradyarrhythmia, resulting in low cardiac output and low blood supply to multiple organs, including the kidney. This condition further impaired the kidney function in regulating potassium levels and cause hyperkalemia. Hyperkalemia, in return, can also cause bradycardia, and the vicious cycle goes on and on. Previous studies reported that calcium gluconate administration might significantly improve the patient's condition. However, in this case, calcium gluconate failed to give significant improvement even though it reduced the potassium level. We report a 53 years old male patient on carvedilol with bradyarrhythmia, chronic kidney disease, shock, and hyperkalemia (BRASH syndrome) that failed to resolve with calcium gluconate administration.

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INTRODUCTION

Chronic kidney disease patient is common presented with hypertension in a clinical setting. Hypertension may act as both; the cause and effect of chronic kidney disease (Pugh, Gallacher, and Dhaun, 2020). Published guidelines suggested several drugs for hypertension control, one of which is beta-blocker. Compared to other beta-blockers, carvedilol is considered to be safer (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2012). However, attention should be paid to the beta-blockers side effect, which is AV nodal block that causes bradycardia and low cardiac output. These conditions resulted in further impairment of renal function that provoked hyperkalemia because of impaired potassium clearance. Leaving these conditions unnoticed and untreated may be life-threatening (Bianchi *et al.*, 2019). While managing these conditions with the bradycardia algorithm was ineffective (Farkas *et al.*, 2020). We reported a case of 53 years old male on carvedilol for hypertension presented in the emergency room (ER) with junctional bradycardia, chronic kidney disease on hemodialysis, shock, and hyperkalemia (BRASH syndrome) that failed to resolve with calcium gluconate administration.

CASE REPORT

A 53 years old male was presented to the ER with fatigue. No dizziness or syncope episode was reported. The patient was previously diagnosed with chronic kidney disease and had been on routine dialysis. He was on carvedilol 6.25 mg bid for hypertension and admitted that there was no change in the dosage. His pulse was 40 bpm, and blood pressure was 70/50 mmHg during admission. No abnormality was found during other physical examinations. The initial 12 lead electrocardiography (ECG) showed junctional rhythm with normal axis and 40 bpm heart rate with normal QTc 405 ms (figure 1). The echocardiography showed a preserved ejection fraction of 55% with a low velocity-time integral of 15 cm and low cardiac output of 2.6 liters/minute. A routine swab test was done and showed a negative result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Laboratory findings showed significant result in potassium (6 mEq/L, normal range 3.6 - 5.2 mEq/L) and creatinine (8.8 mg/dL, normal range 0.7 - 1.2 mg/dL). The patient was diagnosed with BRASH syndrome. Two grams of calcium gluconate (2 attempts, 1 gram each attempt) were given as the initial treatment. The potassium decreased to 4.6 mEq/L, but the patient remains bradycardia. Thus, dobutamine and epinephrine in combination were given to the patient. The patient was transferred to the intensive care unit to be closely monitored. However, the patient's condition deteriorated even after receiving the maximum dose of dobutamine and epinephrine. The patient was pronounced dead after four days of treatment in the hospital.

DISCUSSION

The incidence of BRASH syndrome is currently unknown because it is previously not reported as an entity. Patients with BRASH syndrome should be differentiated from other bradyarrhythmia patients because the two bradycardia cases' management is different (Farkas *et al.*, 2020). In several studies, patients with BRASH syndrome reported dizziness, a history of syncope, weakness, difficulty breathing, and altered mental status as their chief complaint. In this case report, our patients only reported fatigue as his chief complaint. Our patient admits that he was taking carvedilol 6.25 mg bid for his hypertension without any dosage change. Thus, we can exclude intoxication with AV-nodal blocking agents, which is closely related to supratherapeutic drug levels. At the same time, BRASH syndrome occurred when there is a synergy between therapeutic drug levels and hyperkalemia (Farkas *et al.*, 2020).

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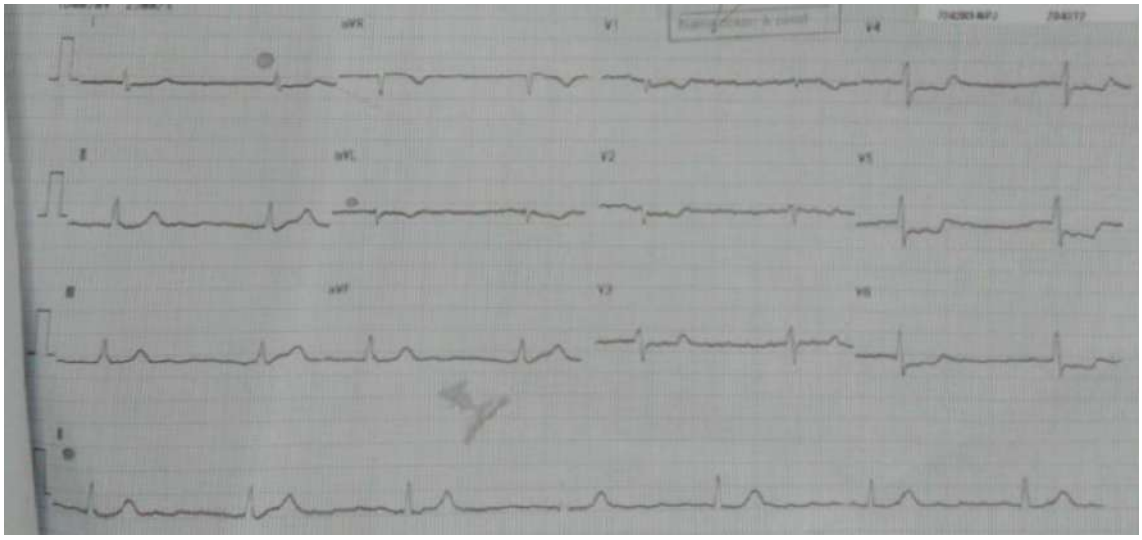

Figure 1. The 12 lead ECG of the patient during admission with junctional bradycardia

Carvedilol is a beta-blocker commonly used in managing hypertension, and it is reported to be safer than its beta-blocker predecessor. However, safer does not mean that it is free of side effects (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2012). Its usage had also been reported in patients with BRASH syndrome in two previous studies, even though in both studies, carvedilol was not only consumed by the patients (Erden, Yalcin, and Ozhan, 2010; Aziz *et al.*, 2011). Besides carvedilol, other drugs such as verapamil, amlodipine, trimethoprim-sulfamethoxazole, digitalis, Angiotensin-converting enzyme inhibitors (ACE-inhibitors), Angiotensin II receptor blockers (ARBs), and other beta-blockers (propranolol, metoprolol, atenolol, and sotalol) was also reported to be taken by BRASH syndrome patients (Farkas *et al.*, 2020).

Hyperkalemia can occur with several mechanisms: 1) excessive intake, 2) impaired elimination of potassium, and 3) increased shift of potassium from intra to extracellular space (Lehnhardt and Kemper, 2011). Our patients did not report any additional drug taken besides carvedilol, no change in carvedilol dosage, and no high potassium intake. The cause of hyperkalemia in this patient is most likely associated with the elimination of potassium because he had chronic kidney disease on hemodialysis. Hyperkalemia further compounded bradyarrhythmia and low cardiac output caused by beta-blockers. Low cardiac output caused more impairment to the kidney function, and the vicious cycle continued (Schnaubelt *et al.*, 2020).

The acute bradycardia management algorithm is widely known by healthcare providers, especially those who work in the emergency department. The acute bradycardia management algorithm suggested that the first step in treating bradycardia is by administering atropine sulfate, but the algorithm did not mention administering calcium gluconate (Kusumoto *et al.*, 2019). Atropine sulfate was proven to be ineffective in managing bradyarrhythmia in BRASH syndrome patients. On the contrary, calcium gluconate was proven to give a significant clinical response to the patients (Farkas *et al.*, 2020). Besides reducing potassium levels, calcium gluconate can stabilize the myocardium to increase heart rate, which correlates to more cardiac output (Farkas *et al.*, 2020). We have managed our patients with two calcium gluconate administration

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attempts (1 gram each), but the patient's clinical condition did not improve. Long B et al. recommended that calcium chloride via central access be administered after two failed calcium gluconate administration attempts. The next step is to enhance the redistribution of potassium by administering insulin and glucose, beta-agonists, and bicarbonate. However, in patients with chronic kidney disease on hemodialysis, only insulin administration could significantly lower potassium levels (Long *et al.*, 2018). We did not administer calcium chloride via central access, insulin, and glucose in this patient because the potassium level has decreased to 4.6 mEq/L.

Currently, no guideline specifically discusses the management of BRASH syndrome. However, a literature review based on several case reports concluded that BRASH syndrome management could be grouped into four major groups: potassium correction, fluid resuscitation, kaliuresis (with/without dialysis), and catecholamine for bradycardia and shock (Farkas *et al.*, 2020).

Potassium corrections have been discussed previously. Fluid resuscitation was not done in this patient due to his previous medical condition (chronic kidney disease on hemodialysis). Hemodialysis should have been done in this patient because hemodialysis can help reduce potassium levels. However, we did not perform hemodialysis on this patient because the potassium levels have decreased after administering calcium gluconate. We have maximized our attempt in managing the bradycardia and shock using catecholamine with a combination of epinephrine and dobutamine and still failed to improve the patient's condition. The transvenous pacemaker was not necessarily used to managed BRASH syndrome patients (Farkas, 2016). Besides, the hospital facility was not possible to conduct transvenous pacemaker implantation, so a transvenous pacemaker was not used in this case. Furthermore, the referral was not performed because of the non-transportable condition of the patient.

CONCLUSION

Chronic kidney disease patients, especially on hemodialysis, should be monitored closely when prescribed, even with a single agent that can block AV nodal. In managing bradyarrhythmia patients, BRASH syndrome should be considered because it cannot be managed with the existing acute bradycardia management algorithm. Considering the complex situation of BRASH syndrome, which needs close monitoring and the possibility of needing hemodialysis and transcutaneous pacing, patients with BRASH syndrome could not be adequately managed in primary care settings. They should be referred as soon as possible to a complete facility, a hospital with a heart center is preferable. Calcium gluconate should be administered as the first-line treatment and can be repeated. The patient that failed to resolve the patient could be treated with calcium chloride via central access, insulin administration, hemodialysis, and catecholamine. A transvenous pacemaker was not necessarily used in managing BRASH syndrome patients but can be considered when all attempts have been made.

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Case Report

Management and quality of life extranodal non hodgkin lymphoma of testis

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ABSTRACT

Extranodal non-Hodgkin lymphoma still seems to be a rare case and an issue to discuss a lot. Clinical evidence and guidelines on treatment have not yet been widely published and accessible. We present a case of a forty-five-year-old male with the chief complaint of a bulky and huge right mass in the testis with an ulcer on it. The patient underwent an orchiectomy, and the biopsy showed a malignant round cell tumor, suspected as non-Hodgkin lymphoma. The patient then received the following treatment: chemotherapy with R-CHOP regiment every three weeks, consisting of 6 cycles showing shrinkage size of the testis by day 7 and final complete response after 4th cycle with ADE grade 0 no sexual activity disorder after chemotherapy. This raises hope in developing treatment modalities that the right choice on chemotherapy regimen with complete control on the drug effects may improve clinical outcome and patient's quality of life.

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INTRODUCTION

Extranodal Non-Hodgkin lymphoma (NHL) is an uncommon case. Approximately 30% of NHL are extranodal, which can arise from any organ. The most common extranodal lymphoma originates from the GI tract (4-20% cases). NHL of the testis is 1-9% of all cancer cases and 1-2% of NHL cases. The mean age of patients diagnosed with extranodal NHL is 63 years old and 66-68 years for NHL of the testis (Cheah, Wirth, & Seymour, 2014; Nanthakwang et al., 2019; Vannata & Zucca, 2015; Xu & Yao, 2019).

Extranodal NHL is mostly found during an advanced stage and on immunocompromised patients. It is a progressive and bulky disease that often reoccurs, has a poor prognosis, and rarely responds completely (Vannata & Zucca, 2015). Nevertheless, this report will discuss the diagnostic approach and therapy modalities in a young, sexually active man, followed by monitoring FSH and LH due to the awareness of NHL-induced secondary hypogonadism.

CASE REPORT

Forty-five-year-old male, married with two children, who lived in Lamongan, East Java, presented with a bulky and massive right mass testis, 20x20 cm in size, with an ulcer since four months ago. He lost approximately 13 pounds in 2 months. He did not have any history of hypertension, diabetes mellitus, or previously known malignancy. He had not been smoking for a year back and had no alcohol intake since married.

In May 2019, he came to a private hospital in Lamongan, East Java. The USG testis showed a solid mass with a solid line, positive vascularization, size 11 x 8,7 x 12,9 cm, suspect testicular tumor, suspicious metastatic process lymphadenopathy of right and left inguinal (Figure 1).

Figure 1. Four dimension USG of Testicle

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Figure 2a

Figure 2b

Figure 2c

Figure 2d

Figure 2a-d. MSCT demonstrated enhancing homogenous mass with the necrotic area, solid line, size 8,6x11,6x15 cm in the right scrotum, suspect testicular tumor multiple lymphadenopathy paraaortic size 1,3x1,5x2 cm, right inguinal 1,7x1,2x0,98 cm, left inguinal 1x1,5x1,6 cm

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Tumor marker level of germinal cell tumor showed normal (LDH 565 U/L; β-HCG < 0.6 mIU/ml; AFP 1.42 IU/Ml); and not detected hepatitis viral and HIV infection (HbsAg negative; anti-HCV negative; and HIV test negative). MSCT demonstrated enhancing homogenous mass with a necrotic area, suspected testicular tumor multiple lymphadenopathies, and inguinal (Figure 2a-d).

Orchiectomy unilateral right-sided testis was performed in June 2019 in a private hospital, and biopsy results showed suspect non-Hodgkin lymphoma. After orchiectomy, the mass became larger with an ulcer, and the patient was then referred to Dr. Soetomo General Hospital, Surabaya, East Java, for further diagnostic process and treatment.

IHC result showed CD 20+ Ki index proliferation 30%, confirming NHL B cell type high grade. The patient was treated using the R-CHOP regiment every 21 days and six cycles. The evaluation was done after the first cycle of chemotherapy on day 7th showed shrinkage size of testis and no blood or pus found in the scrotal ulcus. After 4th and 6th cycle chemotherapy, the patient showed complete response with Adverse Event Drugs (ADE) grade 0. Evaluation level of FSH, LH, and Testosterone was performed after chemotherapy, mean level of FSH 39,48 mIU/ml, LH 16,59 mIU/ml, testosterone 165,12 ng/dl. No sexual activity disorder was found after chemotherapy. Radiotherapy was not performed for the patient.

DISCUSSION

NHL of the testis is an example of extranodal NHL, which is scarce and aggressive. According to Surveillance, Epidemiology, and End Results (SEER), the median age of patients with NHL of the testis is 70 years old. Histological subtype NHL of testis most commonly demonstrate diffused large B cell lymphoma (DLBCL) 82,9% and 68,6% of patients are diagnosed in early-stage (stadium I-II), 5% in stadium III, and 15,9% in stadium IV. Most frequent cases are found in the right-sided testis (49,1%) and rarely bilateral (5,3%). NHL of the testis is commonly found in Caucasians (Kuper-Hommel et al., 2012; Xu & Yao, 2019).

NHL of the testis is sometimes associated with hydrocele. Constitutional symptoms at admission are uncommon. They strongly suggest systemic disease in 20% to 30% of patients (Ellatif, Kumar, Weller, Katz, & Vrentzou, 2019; Nanthakwang et al., 2019; Sahu, Mishra, Lal, & Oshea, 2020; Shih et al., 2014; Xu & Yao, 2019).

Ultrasound of gonadal NHL demonstrated enlarged, heterogenous, and hyper-vascular testicles. Tunica albuginea and epididymis are infiltrated and presenting a hydrocele. The ultrasound imaging of epididymis and testis reveals hypervascularity and infiltrative mass; however, it will be excluded by orchiectomy and biopsy. CT demonstrated testicular mass with soft tissue extending along the spermatic cord through the inguinal canal and cranially in the retroperitoneum along the gonadal vein to the level of its insertion into the inferior vena cava. It also infiltrated organs around the testis. Sporadic lymph node involvement and extranodal deposit finding in CT and ultrasound are strongly associated with lymphoma, infection, or germ cell tumor (Ellatif et al., 2019).

Modality of treatments of NHL of the testis is surgery, chemotherapy, immunotherapy, and radiotherapy. Inguinal orchiectomy and debulking surgery aim to control the disease growth and simultaneously get pathological specimens as a diagnostic tool. Histo-pathologically, the NHL of testis shows a large lymphoid cell with the size of nucleus

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twice normal nucleus lymphocyte and no Reed Stenberg cell. It is challenging to distinguish NHL of testis from seminoma histopathologically since they look alike; however, Immunohistochemistry (IHC) will be useful to verify the diagnosis. IHC used to diagnose lymphoma is CD 20 and Ki67. The Ann Arbor system is used to stage NHL (Cheah et al., 2014; Marcus, Sweetenham, & Williams, 2014).

A standard treatment for NHL of testis has not yet been established since it is a rare disease and prospective randomized controlled trials were not yet available. In previous studies for NHL of the testis, orchiectomy has been used as a diagnostic and a therapeutic tool; however, the outcomes of patients who undergo this surgery alone or in combination with radiotherapy are not satisfactory (Xu & Yao, 2019).

Following the introduction of Rituximab in 2006, the prognosis of patients' NHL of testis has significantly improved. A retrospective review involving 75 patients with NHL of testis from MD Anderson Cancer Centre revealed that the addition of Rituximab to anthracycline-based chemotherapy significantly improves the 5-year overall survival. In addition, a retrospective analysis by the British Columbia Cancer Agency demonstrated that the five-year-progressive-free survival (PFS) and OS of patients treated with Rituximab were similar (Jia et al., 2014; Xu & Yao, 2019).

Chemotherapy regiment used to NHL of testis mainly are CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). There are some conditions that, if CD 20 results positive, Rituximab will be given every 21 days for 6-8 cycles. The regiment came with or without prophylaxis for the central nervous system, methotrexate, administrated intravenously or intrathecally. The regiment comes with the recommended dose, which is: Rituximab 375 mg/m^2; Cyclophosphamide 750 mg/m^2; Doxorubicin 50 mg/m^2, and Vincristine 1.4 mg/m^2; The other NHL of testis regiment for patients 18-60 years old are VCAP (vindesine, doxorubicin, cyclophosphamide, prednisolone), VECP-bleo (vindesine, epirubicin, cyclophosphamide, prednisolone, bleomycin), or R-CEOP (Rituximab, cyclophosphamide, epirubicin, vincristine, prednisone) every 14 days (Cheah et al., 2014; Marcus et al., 2014; Skeel & Khleif, 2011).

A single-center study in China showed a complete response of stadium I NIHL subtype DLBCL after 4-6 cycles of R-CHOP or CHOP. Most patients at stage II had demonstrated partial response for 6-8 cycles using CHOP or RCHOP. Progressive disease and partial response were seen in stadium III and IV. International Prognostic Index (IPI) ≤ 1 in the stadium I and II refer to complete response and better prognosis (Jia et al., 2014; Zhou et al., 2017).

A new study using SEER data from 1,165 NHL of testis cases from 1973 to 2013 had demonstrated the 5-year cause-specific survival (CSS) rates improving significantly after the Rituximab era (after 2006), 44% during 1973-99, 62,4% during 1998-2005, and 70,4% during 2006-2013, respectively. Patients under 70 years old that are diagnosed and treated earlier show a more promising prognosis. The 5-year CSS rates were 60,2% for DLBCL, 57,8% for indolent B-NHL, 40,4% for other aggressive B-NHL, and 53,4% for malignant NHL that was not otherwise specified. All patients underwent surgical intervention, and patients who had received radiotherapy had a five-year CSS rate of 67,5% compared with 54,3% for patients who did not undergo radiation therapy. According to stadium NHL of testis, the 5-year CSS and OS of stadium I is (70.9% & 70.5%); stadium II (58.2% & 58.1%); stadium III (48.1% & 49%); and stadium IV (34.7% & 35.5%) (Deng et al., 2016; Xu & Yao, 2019).

In the DLBCL subtype, Rituximab had been

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remarkably improving the prognosis of stage I-IV. Patients at the earlier stages who receive Rituximab manifest better outcomes and prognosis. The complete response showed in the early stages (stages I and II), but no data represented the long-term effect of chemotherapy (Ma et al., 2018; Xu & Yao, 2019).

The effect of orchiectomy and chemotherapy for infertility and the occurrence of hypogonadism in NHL of testis patients is debatable. The orchiectomy unilateral showed some dynamic effects in fluctuating FSH, LH, and testosterone hormones in patients with tumor testis. However, a study from Wiechno et al., 2017, did not include NHL of the testis as a sample; therefore, there is still not enough evidence on infertility and hypogonadism following NHL of the testis. Nevertheless, RCHOP or CHOP regiment < 8 cycles demonstrated lower gonadotoxic effect and impaired quality of sperm (Kumar et al., 2018). However, a satisfying result has been seen in a patient showing complete response to the therapy with grade 0 adverse drug effect (ADE) and normal gonadal hormones. The absence of disturbance in the sexual activity was also paramount considering the patient's quality of life.

CONCLUSION

Testicular LNH has been reported in a 45-year-old male. He was diagnosed with LNH B cell type high-grade CD 20 + with stage II EB. A right unilateral orchiectomy was performed, the mass still enlarged and formed a scrotal ulcer after orchidectomy, and then chemotherapy followed. The chemotherapy regiment used was a 6-cycle R-CHOP regimen every 21 days. After six cycles of chemotherapy, complete therapeutic response with an ESO grade 0 was gained. There were no signs of hypogonadism, and the FSH, LH, and testosterone levels were within normal limits. No disturbance of sexual activity was reported.

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Case Report

An anomalous neural interconnection between the Lingual and Mylohyoid Nerves

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ABSTRACT

The interconnection between the lingual nerve (LN) and the hypoglossal nerve, the LN and the inferior alveolar nerve (IAN), and the LN and the mylohyoid nerve (MHN) has already been documented in the literature. Despite the fact that variations in the course of the MHN in regard to the mandible are regularly observed, they have yet to be well documented in the anatomical or surgical literature. This anatomical variety necessitates that surgeons and anesthesiologists who routinely perform oro-surgical interventions and nerve blocks in the face for various neuralgias enhance their knowledge and awareness in order to avoid unintended nerve injury. In the present case report, we observed an aberrant neural loop connecting LN and MHN, as well as anatomical insight into an integrated component of MH along with LN in addition to the motor component.

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INTRODUCTION

The mylohyoid nerve (MHN) is a branch of the inferior alveolar nerve (IAN), which rises above the mandibular foramen (Potu et al., 2010). The MH supplies motor innervation to the mylohyoid and anterior belly of the digastric muscle (Clark et al., n.d.). The mylohyoid muscle plays an essential role in chewing, swallowing, respiration, and phonation (Ren & Mu, 2005). The lingual nerve (LN) is a branch of the posterior division of the mandibular nerve. It is sensory to the anterior 2/3rd of the tongue (Kumar et al., 2021).

Lingual nerve lesion is a common side effect of several oral and maxillofacial surgery surgeries (LN). It may be injured during third molar extraction, periodontal treatments, mandibular trauma management, and excision of neoplastic tumors due to its anatomical placement (Behnia et al., 2000; S Y Kim et al., 2004). A needle puncture during local anesthesia or suture may also cause LN injury. The leading cause of this issue is the LN's anatomic variability and surgeons' difficulty pinpointing its precise position (Behnia et al., 2000).

Previous literature has reported communication between LN and hypoglossal nerve (Kumar et al., 2021), LN and IAN (Sandoval et al., 2009), and also LN and MHN (Jha & Khorwal, 2018; Potu et al., 2010; Sato et al., 2004; Thotakura et al., 2013). Although variations in the course of the MHN in relation to the mandible are frequently found during routine dissection, they have not been satisfactorily described in the anatomical or surgical literature (Kim et al.,2004). In the present case report, we discovered an aberrant neural loop connecting LN and MHN, as well as anatomical insight into an integrated component of MH along with LN in addition to the motor component.

CASE REPORT

In this case report presented, a 65-year-old male cadaver was dissected following preservation in a 10% formalin solution. The lateral side of the face was gently dissected by lifting up the parotid gland with the duct, then the masseter muscle was reflected, and a portion of the ramus of the mandible was cut and removed to approach the infratemporal fossa, where the lingual nerve, inferior alveolar nerve, and mylohyoid nerve were exposed. While tracing the IAN and MHN, an unusually narrow neural connection between the MHN and LN was noticed (Figure 1).

In the left side, the MHN gave a short communicative branch that joined the LN (second part) around the level of the intermediate tendon of the digastric muscle. The distance between the place where the connecting branch emerged from the mylohyoid and the origin of the mylohyoid from IAN was 29.4 mm. The length of the communicating branch which extended from MHN to LN was 31.7 mm.

Measurements was recorded using a Vernier caliper. The MHN and LN followed their typical path and branching pattern. No additional variation was discovered along the course of IAN or LN origin and its branches.

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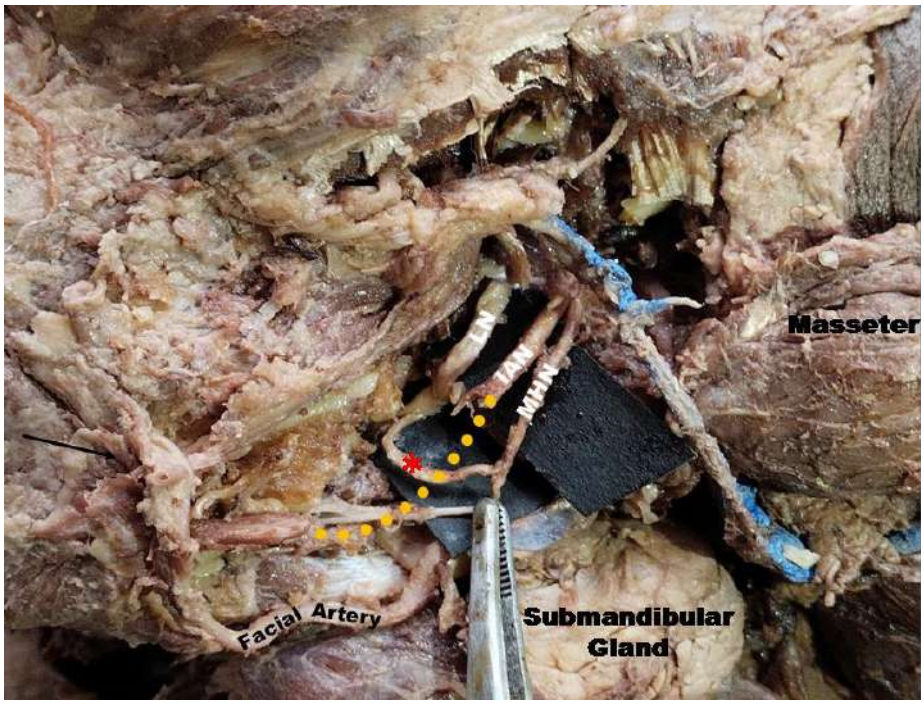

Figure 1. showing the nerve interconnection between MHN and LN (Asterisk *). LN- Lingual nerve, MHN- Mylohyoid nerve, IAN- Inferior alveolar nerve.

DISCUSSION

Previous studies have reported the incidence of neural interconnection between IAN and LN, justifying this communication as the cause for insufficient mandibular anesthesia (Kim et al.,2004). According to Kumar JM et al. (2021), the course of the lingual nerve could be studied under three distinct segments. The first segment extends from the root to the third molar tooth; the Second segment from the third molar tooth to the point where branches branch off to the submandibular ganglion; and the third segment from the end of the second segment to the point where it enters the tongue. We observed the communicating nerve loop in relation to the second segment of the LN.

Variation in the mylohyoid nerve might occur at the point of origin, along its course, or at the level of innervations. The MHN origin variant has been described in the literature. In 10% of instances, the MHN arises from the trunk of the mandibular nerve (Kumar et al., 2011), and in some instances, it arises as two roots, one root from the mandibular nerve and another from IAN (Nayak & Soumya, 2020). In addition to that, it may arise as a branch of the glossopharyngeal nerve or lingual nerve (Tubbs et al., 2016) as well as within the mandibular canal (Nayak and Soumya, 2020). It's possible that the inferior alveolar nerve can supply an additional MHN (Jha & Khorwal, 2018).

The nerve may take a variety of paths, including its passage through lingual foramina in the midline of the mandible. It may have a various course running in the mandibular canal and exiting through a foramen (Choi et al., 2019), it may pass through accessory foramen below premolars and end by supplying premolar teeth (Benett and Townsend, 2001) or communicate with the lingual nerve close to the digastric tendon (Sato et al., 2004). Innervations of MHN may differ in the following ways: 60% of patients may have premolar, canine, and incisor teeth that are innervated by this nerve

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(Heasman & Beynon, 1986). It may also innervate the submandibular gland (Varol et al., 2009) and the lower lip as cutaneous innervation (Benett & Townsend, 2001), as well as the skin of the submental region as Valentins nerve (Choi et al., 2019), and the mylohyoid muscle as duplicated innervation (Jha & Khorwal, 2018).

During our literature research, we discovered that the findings of one study suggested the presence of both motor and sensory neurons in MHN (Frommer & Monroe, 1972). Because of the aforementioned reason, a traditional inferior alveolar block may be inefficient in inducing mandibular anesthesia, as is evident in the current case report (Jha & Khorwal, 2018). The incidence of neural interconnection between MHN and LN may vary from 1.45% to 46.3%, in addition to a few case reports documenting them as isolated incidental cadaveric findings (Table 1). The highest incidence of this anomalous loop has been reported by Kameda et al. (46.3%) followed by Racz et al. (33.3%). The latter also coined the term sublingual curl for this loop.

nerve is susceptible to injury during tooth extraction and other dental procedures due to its proximity to the molar tooth (second part of LN). By providing additional innervation, this communication loop may function as a healing point for the lingual nerve once it has been injured (Racz Vl et al., 1981; Al-amery et al., 2016). As per a literature review, this communicating branch has a developmental basis and is implicated in coordinating tongue movements with suprahyoid muscles through proprioceptive impulses from the mylohyoid muscle to the lingual nerve.

Table 1. Incidence of interconnection between mylohyoid and lingual nerve in different studies

Authors, Year	No of specimens	Gender	Side	Incidence
Kameda et al., 1952	160 Specimens	-	-	46.3%
Racz et al., 1981	48 Specimens	-	-	33.3%
S Y Kim et al., 2004	32 Specimens	-	-	08%
Sato et al., 2004	413 Specimens	Male: 2 Female: 4	Bilateral	1.45%
Sandoval et al., 2009	01 cadaver	Male	Unilateral	Case report
Potu et al., 2010	01 cadaver	Male	Unilateral	Case report
Thotakura et al., 2013	36 Specimens	Male Female	Bilateral Unilateral	8.33%
Kaur et al., 2014	01 cadaver	Male	Bilateral	Case report
Sinha et al., 2014	01 cadaver	Female	Unilateral	Case report
Kumari S et al, 2015	01 cadaver	Male	Bilateral	Case report
Premakumari & Dnyaneshwar, 2018	40 Specimens	-	Bilateral	2.5
Jha & Khorwal., 2018	01 cadaver	Male	Unilateral	Case report
Present report, 2021	01 cadaver	Male	Unilateral	Case report

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CONCLUSION

Most neural interconnections involving the MHN and LN have been documented as case reports. Very few studies are available. Hence, more studies need to be carried out to elucidate the true incidence of the above said neural interconnection. This anatomical variety necessitates that surgeons and anesthesiologists who routinely perform oro-surgical interventions and nerve blocks in the face for various neuralgias enhance their knowledge and awareness to avoid unintended nerve injury.

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