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Original Article

THE DIFFERENCE IN NEUTROPHIL-LYMPHOCYTE RATIO (NLR), PLATELET-LYMPHOCYTE RATIO (PLR), AND LACTATE LEVELS BETWEEN SEPSIS AND SEPTIC SHOCK PATIENTS WHO DIED IN THE ICU

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ABSTRACT

Introduction: Sepsis and septic shock are organ dysfunctions caused by the dysregulation of the body's response to infection and are the most common causes of death. **Objective:** This study aims to describe the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in patients with sepsis and septic shock who died in the Intensive Care Unit (ICU). **Materials and Methods:** An observational retrospective study was conducted by examining the medical record data of sepsis and sepsis shock patients who were hospitalized in the ICU of Dr. Soetomo General Academic Hospital Surabaya from January to December 2019. **Results:** The study sample was 28 patients: 16 with sepsis and 12 with septic shock. Fifteen patients (53.6%) were women. The patients' mean age was 53.18 ± 13.61 years, and most patients (8 patients, 28.6%) belonged to the late adult age group (36-45 years). The most common comorbidities were diabetes mellitus and hypertension (30.8%). The highest incidence of infection in both groups occurred in the lungs (42.9%). Most of the patients had high SOFA scores, in the moderate (7-9) to severe (≥ 10) category (39.3%). Almost all patients (82.1%) were treated for less than one week. The hematological examination within the first 24 hours showed a leukocyte value of 16,995 (Leukocytosis) and a platelet value of 279,500 (Normal). The NLR of septic shock patients (31.38±55.61) was higher than the NLR of sepsis patients (23.75±22.87). The PLR of septic shock patients (534.02±1000.67) was lower than the PLR of patients (802.93±1509.89). Lastly, the lactate levels in septic shock patients (3.84±1.99) were higher than in sepsis patients (1.97±1.06). **Conclusion:** There were no significant differences in the NLR and PLR values between sepsis and septic shock patients, but there were significant differences in their initial lactate levels.

Keywords: Died; ICU; Lactate Levels; Neutrophil-Lymphocyte Ratio; Platelet-Lymphocyte Ratio; Sepsis; Septic Shock

ABSTRAK

Pendahuluan: Sepsis dan syok sepsis merupakan disfungsi organ akibat gangguan regulasi respon tubuh terhadap infeksi dan menjadi penyebab kematian terbanyak. **Tujuan:** Penelitian ini bertujuan mengetahui gambaran rasio neutrofil-limfosit, rasio trombosit-limfosit, dan kadar laktat pada pasien sepsis dan syok sepsis yang meninggal di *Intensive Care Unit* (ICU). **Bahan dan Metode:** Studi observasional retrospektif dilakukan pada rekam medis pasien sepsis dan syok sepsis yang meninggal di *ICU* RSUD Dr. Soetomo Surabaya Januari-Desember 2019. **Hasil:** Sampel penelitian sejumlah 28 pasien, yaitu 16 pasien sepsis dan 12 pasien syok sepsis. Lima belas pasien (53,6%) adalah perempuan. Rata-rata usia pasien adalah 53,18 ± 13,61 tahun dan sebagian besar pasien (8 pasien, 28,6%) merupakan kelompok usia dewasa akhir (36-45 tahun). Komorbid paling sering ditemukan yaitu diabetes melitus dan hipertensi (30,8%). Kejadian infeksi terbanyak di kedua kelompok terjadi pada organ paru-paru (42,9%). Sebagian besar pasien memiliki skor SOFA terbanyak ditemukan dalam kategori sedang (7-9) hingga berat (≥ 10) (39,3%). Hampir semua pasien (82,1%) dirawat selama kurang dari 1 minggu. Hasil pemeriksaan hematologi dalam 24 jam pertama, memiliki nilai leukosit sebesar 16.995 (Leukositosis) dan nilai trombosit sebesar 279.500 (Normal). Rata-rata NLR pasien syok sepsis (31,38±55,61), lebih tinggi dari rata-rata NLR pasien sepsis (23,75±22,87). Rata-rata PLR pasien syok sepsis (534,02±1000,67), lebih rendah dari rata-rata PLR pasien (802,93±1509,89). Kadar laktat pasien syok sepsis (3,84±1,99) lebih tinggi dari rata-rata kadar laktat pasien sepsis (1,97±1,06). **Kesimpulan:** Tidak ada perbedaan bermakna pada nilai NLR dan PLR antara pasien sepsis dan syok sepsis, namun terdapat perbedaan bermakna pada kadar laktat awal antara pasien sepsis dan syok sepsis.

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Kata kunci: Meninggal; ICU; Kadar Laktat; Rasio Neutrofil-Limfosit; Rasio Trombosit-Limfosit; Sepsis; Syok Sepsis

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INTRODUCTION

Sepsis and septic shock are major health problems related to infection and are the most common causes of death in the intensive care unit. The annual global incidence rate of sepsis in hospitals has reached 31.5 million cases, of which 19.4 million cases are severe sepsis and 5.3 million caused patient deaths (1). Another study in 2002 in 24 countries in the European continent found that 29.5% of severe sepsis and septic shock cases were from 198 Intensive Care Units (ICU). The high mortality rate of patients with sepsis and septic shock poses a challenge for medical personnel regarding the speed and accuracy of the initial management of sepsis, especially while still in the Emergency Unit. The Indonesian Ministry of Health (2017) stated that the mortality rate for patients with severe sepsis in intensive care had reached 32.2% and 54.1% in cases of septic shock (2).

Sepsis is a syndrome caused by the dysregulation of the body's response to infection, resulting in organ dysfunction. Infection is the body's systemic inflammatory response, which consists of releasing pro-inflammatory cytokines. Early recognition of systemic inflammation as a marker of sepsis can guide early treatment and reduce the potential for widespread metabolic/cellular disturbances and the development of septic shock.

Organ dysfunction can be identified by the Sequential Organ Failure Assessment (SOFA) Score. Sepsis is diagnosed if a patient's total SOFA score is ≥ 2 and a patient is said to be in septic shock if a vasopressor is needed to maintain a Main Arterial Pressure or MAP of ≥ 65 mmHg and serum lactate level ≥ 2 mmol/L. A SOFA score of 2 reflects a mortality of approximately 10% in the general hospital population with suspected infection. This mortality rate increases to 40% when the patients experience septic shock (3).

Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) are new inflammatory biomarkers that can act as indicators of sepsis development. Additionally, a hematological profile can be used to determine the early signs of infection and assess treatment response. NLR and PLR are indices used as prognostic tools in several clinical conditions, including sepsis. NLR is a new inflammatory biomarker that indicates shock in septic patients (4). NLR also has a positive, though weak correlation, with the prognostic Sequential Organ Failure Assessemnt score (SOFA) at admission (5,6). Other studies have also shown that a high PLR is associated with an increased mortality rate for sepsis patients (7).

Identifying the factors affecting organ dysfunction precisely and quickly through periodic examinations can shorten the diagnosis time and instigate prompt treatment, thus reducing mortality sepsis and septic shock patients. Based on this background, we conducted a study that described the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in patients with sepsis and septic shock. This study aims to determine the differences in neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in sepsis and septic shock patients who died in the ICU.

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MATERIAL AND METHOD

This observational retrospective study was conducted on all patients with sepsis and septic shock who died at ICU Dr. Soetomo General Academic Hospital Surabaya. This study used the total sampling method to collect secondary data from the medical records of adult sepsis patients aged ≥ 18 years with a diagnosis of sepsis or septic shock who died in the ICU of Dr. Soetomo General Academic Hospital Surabaya from January 1st, 2019, to December 31st, 2019. The data consists of sociodemographic characteristics (age and gender), comorbidities, underlying disease, length of treatment, early SOFA score, hematology profile (early leukocyte and thrombocyte count), and early NLR, PLR, and lactate levels. The NLR is calculated by dividing the neutrophil count by the absolute lymphocyte count. PLR is calculated by dividing the platelet count by the absolute lymphocyte count. The exclusion criteria in this study were patients who were forcibly discharged and patients with incomplete or missing data.

A total of 28 patients met this study's inclusion criteria, consisting of 16 patients with sepsis and 12 patients with septic shock. Data analysis was conducted using SPSS 23.0 for Windows, a descriptive statistical program, and a comparative test analysis. After the normality test was conducted using Kolmogorov's Smirnov/Shapiro-Wilk test, an unpaired T-test/Mann-Whiteney was performed to determine the mean difference of early NLR, early PLR, and early lactate value in the two patient groups. In the statistical test results, p <0.05 indicated a significant difference between the two groups. This research obtained ethical permission and was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya (0883/LOE/301.4.2/IV/2022).

RESULT AND DISCUSSION

Table 1. Distribution of Patient Characteristics

Variable	Description		Mean/ Median
	Group	N (%)	
Gender	Male	13 (46.4)	
	Female	15 (53.6)	
Age*	26-35	2 (7.1)	
	36-45	8 (28.6)	53.18 ± 13.61 (30-78)
	46-55	5 (17.9)	
	56-65	7 (25)	
	>65	6 (21.4)	
Comorbidities	**With comorbidities**	**14 (50)**	
	Heart disease	2 (7.7)	
	Diabetic	8 (30.8)	
	Hypertension	8 (30.8)	
	Autoimmune -Disease	1 (3.8)	
	Stroke	3 (11.5)	
	Kidney failure	3 (11.5)	
	Malignancy	1 (3.8)	
	Without comorbidities	**14 (50)**	
*Note: One patient can have more than 1 comorbidity			
Early SOFA score*	Mild (< 7)	6 (21.4)	
	Moderate (7-9)	11 (39.3)	8.46 ± 2.63
	Weight (≥ 10)	11 (39.3)	
- Septic			7.75 ± 2.73
- Septic Shock			9 ± 2.50
Underlying Disease	Lung	12 (42.9)	
	Cardiovascular	3 (10.7)	
	Urinary Tract	6 (21.4)	
	Digestive tract	2 (7.1)	
	Skin. Bone & Soft Tissue	4 (14.3)	
	Gynaecology	1 (3.6)	
Treatment Length**	< 1 week	22 (82.1)	
	1-2 weeks	3 (10.7)	1 (1-22)
	> 2 weeks	2 (7.1)	
Early Leukocyte **			16.995 (5.250-38.340) / Leucocytosis
Early Thrombocyte**			279.500 (86.000-878.000) / Normal

Note:
* Variable data is normally distributed (based on the results of the Shapiro Wilk Test: p > 0.05) presented in the mean value and standard deviation (SD)
**Variable data is not normally distributed (based on the results of the Shapiro Wilk Test: p <0.05) presented in the median value (min-max)

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The sample in this study were patients with sepsis and septic shock diagnosed clinically and through laboratory-based testing for the SOFA score. The total subjects during the study period were 28 patients who met the inclusion criteria. The 28 patients were divided into two groups: the sepsis group, with 16 patients, and the septic shock group, with 12 patients. The distribution of the patients' general characteristics is shown in Table 1 below.

The results revealed that there were more female patients than male patients, with 15 female patients (53.6%) and 13 male patients (46.4%). In theory, it states that differences regarding sex in sepsis sufferers may occur due to significantly higher levels of anti-inflammatory mediators in women, contributing to their better prognosis. Studies have shown that men diagnosed with sepsis have high TNF-α (pro-inflammatory) levels and significantly low IL-10 (anti-inflammatory) levels, while the opposite is true in women. The increased production of IL-10 until day five after sepsis diagnosis in women is likely to inhibit the production of other inflammatory cytokines from macrophages that are activated by T-helper cells, which has protective abilities and increase the survival rate in septic conditions. Another study also showed that low 5a-DHT (dihydrotestosterone) and high estradiol levels protected host cells after adverse circulatory conditions, such as septic shock (8).

However, in this study, data for the sex characteristic did not allow the authors to identify the cause of this increase in sepsis and septic shock incidence in female patients. This result may be due to differences in each individual's other vulnerability risk factors (such as nutritional status). It may also be due to the level of care, which is one of this research's limitations. Thus, further research is needed.

The mean age of the patients was 53.18 ± 13.61 years, where the lowest age was 30 years, and the highest was 78 years. A total of 8 patients (28.6%) were in the late adult age group (36-45 years). Individuals in late adulthood are more often treated in health services. Moreover, in this age range, there may also be a decrease in the body's defense system, causing the body to be more susceptible to diseases (9).

The most common comorbidities found in patients with sepsis and septic shock were diabetes mellitus and hypertension (30.8%). The number of comorbidities that increase the risk of death for sepsis patients varies, depending on the underlying infection or pathogen causing the etiology (10). However, factors regarding infecting pathogens based on culture results were not investigated in this study, which is another limitation of this study. The number of comorbidities a patient has can also increase the development of sepsis, although not all comorbidities can increase the risk of death (11–13).

Next, most patients had high SOFA scores in the moderate (7-9) to severe (≥ 10) category (39.3%). This indicates that most patients diagnosed with sepsis in the ICU of Dr. Soetomo General Academic Hospital Surabaya were in quite bad condition, which may be related to the patient's conditions as referral patients. The mean initial SOFA score of sepsis and septic shock patients was 8.46 ± 2.63. Meanwhile, the average SOFA score of sepsis patients was lower than that of septic shock patients, at 7.75 ± 2.73, and septic shock patients at 9 ± 2.50. This is because patients with septic shock need vasopressors to maintain Main Arterial Pressure or MAP ≥ 65 mmHg, which can lead to high SOFA values in

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the criteria for assessing cardiovascular function in septic shock patients (14).

The highest incidence of infection (underlying disease) in both groups occurred in the lungs or respiratory system (42.9%). A theory explains that the incidence of septic shock caused by an infection of the respiratory system is influenced by the length of stay and the use of a ventilator (15). The use of the same ventilator for a long time also increases the opportunity for the development of various pathogens that can cause nosocomial infections. However, this study did not collect data regarding the use of ventilators. Nevertheless, special attention regarding the condition of the treatment room is required to reduce the chance of septic shock and reduce mortality.

Next, almost all patients (82.1%) were treated for less than one week. Other research shows that the results of a patient's diagnosis, when admitted to the hospital can affect the treatment duration, and no other risk factors affect the treatment duration of more than five days (16). From the data from this study, it was also found that there were no septic shock patients who underwent treatment for >2 weeks in the hospital. This is probably because the patient's condition was already severe when admitted and treated in the ICU at Dr. Soetomo General Academic Hospital Surabaya. The incidence of septic shock can affect survival time during treatment. However, data regarding patient referrals or patient conditions before being referred from previous health facilities were not investigated in this research, which is a limitation of this study.

The haematological examination from the first 24 hours found a leukocyte value of 16,995 (leucocytosis). The high leukocyte value is caused by increased leukocyte activity within 24-48 hours from increased levels of pro-inflammatory cytokines. The body's immune response is only balanced if anti-inflammatory cytokines match cytokine production within 24 hours after the pathogen infection. Meanwhile, the platelet count of patients with sepsis and septic shock was 279,500 (Normal), where the lowest value was 86,000, and the highest value was 878,000. This may be because not all sepsis patients experienced complications with DIC (Disseminated Intravascular Coagulation). According to the 2005 PAPDI guidelines regarding laboratory results on assessing the body's haemostatic function due to DIC, even if all patients experience complications of DIC, the platelet count can appear normal in both the compensation and hyper-compensation phases (17).

Table 2. The Comparison of NLR, PLR, and Lactate Levels in Sepsis and Septic Shock Patients

Variable	Septic N = 12	Septic Shock N = 16	p-Value
NLR	23.75 ± 22.87	31.38 ± 55.61	0.908
PLR	802.93±1509.89	534.02±1000.67	0.246
Lactate	1.97 ± 1.06	3.84 ± 1.99	0.002

Note: Asymp. Sig. (2-tailed) *p Value* < 0.05 was considered to have a significant difference between the two groups

Based on the test results in Table 2, there is no significant difference in the NLR (p-value = 0.908) and PLR (p-value = 0.246) in sepsis and septic shock patients. This may be due to the initial process of pathogenesis in sepsis and septic shock, where there is an inflammatory process in which neutrophils, lymphocytes, and platelets can still increase or decrease. When the body responds to inflammation through T lymphocytes that secrete Th1 substances to release proinflammatory cytokines, IFN γ will also stimulate macrophages to release IL1 and TNF α. This results in increased levels of proinflammatory cytokines. However, the body's immune response can become unbalanced if anti-

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inflammatory cytokines does not match cytokine production within the first 24 hours of pathogen infection. This condition can cause the infection to spread throughout the body, resulting in systemic inflammation and sepsis. Then, within 24-48 hours of pathogen exposure, the influence of various mediators and cytokines causes the endothelium to become increasingly stressed, such that the vascular wall loses its function and elasticity, giving rise to signs of septic shock (18–20).

Other results in Table 2 showed a significant difference between the average initial lactate levels in sepsis and septic shock patients. In septic shock patients, the average was 3.84 ± 1.99, whereas, in septic patients, the average lactate level was lower at 1.97 ± 1.06 (p = 0.002). This is because a physiological response in the body leads to lactic acid acidosis. The level of lactic acid in the blood increases in septic conditions through a different mechanism than septic shock. Hyperlactatemia in sepsis is caused mainly by excessive hypermetabolism and lactate clearance that does not match the body's metabolism (21–23). Increased lactate in sepsis can occur due to the increased production of leukocytes and phagocytes, increased production of lactic acid in the lungs, increased production of lactic acid in the splanchnic area due to dysoxia, multiorgan disorders that produce lactic acid, and increased activity of phosphofructokinase. In septic shock, similar conditions, other than hypermetabolism, occur due to extensive tissue hypoxia (22,24).

To overcome this condition, septic shock patients are recommended to be given vasopressor therapy to maintain MAP and monitor lactate levels repeatedly (3,25). However, data related to adherence to sepsis bundle therapy and septic shock in the patients in this study sample were considered homogeneous, which is a limitation of this study. We hope there will be several follow-up studies that can improve this study and fill the research gaps in this topic.

CONCLUSION

The results showed no difference in NLR and PLR between sepsis and septic shock patients. However, there was a significant difference between lactate levels in sepsis and septic shock patients. Patient mortality due to sepsis is still relatively high, especially for patients with septic shock. A multicenter prospective study in Indonesia with serial measurements over a longer period is needed to better understand the characteristics of sepsis and septic shock patients.

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Conflict of Interest

The authors stated that there is no conflict of interest in this study.

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Authors' Contributors

All authors have contributed to all processes in this research.

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Original Article

VALIDATION OF THE APACHE IV SCORE FOR ICU MORTALITY PREDICTION IN DR. SARDJITO HOSPITAL DURING THE PANDEMIC ERA

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ABSTRACT

Introduction: ICU service quality must continuously improve to provide better patient service. One of these improvement efforts is the use of a risk prediction system to predict mortality rates in the ICU by utilizing risk factors. This system helps healthcare services perform evaluations and comparative audits of intensive services, which can also aid with more targeted planning. APACHE IV is considered to have good validity. However, its predictive capabilities may change over time due to various factors, such as the pandemic, where changes in the case mix may affect its predictive abilities. Therefore, this research tests the validity of APACHE IV on the Indonesian population through Dr. Sardjito Hospital patients. The findings can be utilized for future use and risk stratification, and ICU quality benchmarking. **Objectives**: This study aims to assess the validity of the APACHE IV score in ICU Mortality prediction in Dr. Sardjito Hospital for medical patients, surgical patients, and patients with both cases during the pandemic. **Materials and Method**: This study used retrospective data from 336 patients at Dr. Sardjito Hospital Yogyakarta from the 1st of January 2020 to the 31st of December 2021. All data required for calculating the APACHE IV score was collected, and the patient's observed ICU Mortality was used. The model's predictive validity is measured by finding the discrimination and calibration of the APACHE IV score and comparing it to the observed ICU mortality. Validation was also conducted separately for medical and surgical cases. **Results**: APACHE IV shows good discrimination ability in all cases (AUC-ROC 95% CI: 0.819 [0.772-0.866]) but poor calibration (p = 0.023) for mortality prediction in the ICU. For medical cases, the discrimination ability is poor but still acceptable (AUC-ROC 95% CI: 0.698 [0.614-0.782]), and in surgical cases, the discrimination ability is good (AUC-ROC 95% CI: 0.848 [0.776-0.921]). Both cases showed good calibration (p: medical = 0.569, surgical = 0.579) in predicting mortality during the pandemic. **Conclusion**: APACHE IV showed good discrimination but poor calibration ability for predicting mortality for all ICU patients during the pandemic era. Mortality prediction for surgical cases showed good discrimination and calibration. However, medical cases showed poor discrimination but good calibration.

Keywords: Acute Physiology and Chronic Health Evaluation IV; Intensive Care Unit; Mortality; Risk prediction; Scoring system.

ABSTRAK

Pendahuluan: Peningkatan kualitas pelayanan ICU tetap harus dilakukan dengan tujuan untuk memberikan pelayanan yang lebih baik kepada pasien, salah satunya adalah penggunaan sistem prediksi risiko yang berguna untuk memprediksi angka kematian di ICU dengan memanfaatkan faktor risiko. Sistem ini memudahkan pelayan kesehatan untuk melakukan evaluasi dan audit komparatif pelayanan intensif, hal ini juga membantu dalam melakukan perencanaan yang lebih tepat sasaran. APACHE IV dianggap memiliki validitas yang baik, namun kemampuan prediktifnya dapat berubah dari waktu ke waktu karena berbagai faktor seperti pandemi di mana perubahan campuran kasus dapat memengaruhi kemampuan prediksinya. Dengan demikian, layak dilakukan penelitian untuk menguji validitas APACHE IV pada populasi Indonesia sehingga dapat digunakan untuk penggunaan di masa mendatang bahkan dapat digunakan untuk stratifikasi risiko dan pembandingan kualitas ICU. **Tujuan:** Penelitian ini bertujuan untuk mengetahui validitas skor APACHE IV dengan mortalitas ICU pada pasien RSUP Dr Sardjito pada pasien dengan kasus medis, kasus bedah, dan kedua kasus tersebut pada era pandemi. **Bahan dan Metode:** Tiga ratus tiga puluh enam data pasien dimasukkan secara retrospektif dari RSUP Dr. Sardjito Yogyakarta dari 1 Januari 2020 – 31 Desember 2021. Pengumpulan data mencakup semua data yang diperlukan dalam menghitung skor APACHE IV dan Mortalitas aktual ICU pasien. Validitas prediktif model diukur dengan menemukan diskriminasi dan kalibrasi skor APACHE IV dengan membandingkannya dengan mortalitas ICU yang diamati. Validasi juga dilakukan secara terpisah untuk kasus medis dan bedah. **Hasil:** APACHE IV menunjukkan kemampuan diskriminasi yang baik dalam semua kasus (AUC-ROC 95% CI: 0,819 [0,772-0,866]), tetapi kalibrasi buruk (p=0,023) untuk prediksi kematian di ICU. Untuk kasus medis, kemampuan diskriminasinya lemah (AUC-ROC 95% CI:

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0.698 [0.614-0.782]), sedangkan pada kasus bedah kemampuan diskriminasinya baik (AUC-ROC 95% CI: 0.848 [0.776-0.921]). Kedua kasus tersebut masing-masing menunjukkan kalibrasi yang baik (p: medical=0.569, surgical= 0.579) dalam memprediksi mortalitas di era pandemi. **Kesimpulan:** APACHE IV menunjukkan kemampuan diskriminasi yang baik tetapi kalibrasi yang buruk untuk prediksi mortalitas seluruh pasien ICU di era pandemi. Prediksi mortalitas untuk kasus surgical menunjukan diskriminasi dan kalibrasi yang baik. Untuk kasus medical menunjukan kemampuan diskriminasi yang buruk dan kalibrasi yang baik.

Kata Kunci: *Acute physiology and Chronic Health Evaluation* IV; *Intensive Care Unit*; Mortalitas; Prediksi risiko; Sistem skoring

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INTRODUCTION

One of the most important services in a healthcare facility is the Intensive Care Unit (ICU). Therefore, the ICU service quality must be continuously improved to provide better patient service by evaluating the effectiveness of the treatments provided to the patients. A proper assessment of the patient's condition before treatment is needed for a valid therapy evaluation (1). A risk prediction system is one method to evaluate a patient's condition (2). The system is useful for analysing and assessing risk factors that will later be used to predict the prolonged length of stay (PLOS) and mortality rates of ICU patients.

The scoring system can also help healthcare policyholders to manage human resources, time allocation, and the various equipment needed per the needs of ICU patients (3). The benchmark of ICU LOS can be used to evaluate the processes and policies in ICUs. Best practices are related to survival and resource allocation and can be used to monitor advancement in ICU resource allocation in a multiple-hospital system (4). The Ministry of Health's technical instructions for ICU service implementation in hospitals also states that a prognostic prediction system can be used as an indicator for evaluating and monitoring ICUs and assessing their quality of care by comparing predicted mortality and observed mortality. However, a study states that the assessment of APACHE's validity on COVID-19 patients is still not fully studied yet (5).

Studies done during the pandemic with the addition of COVID-19 patients in the setting may bring changes to disease patterns and severity (6), which may lead to different results compared to previous studies. Thus, this study aims to assess the performance of APACHE IV in predicting mortality in ICU patients in Dr. Sardjito Hospital, especially during the pandemic, where changes in the case mix may affect its predictive performance.

MATERIALS AND METHODS

Study Design

This is an observational retrospective cohort study. Data were collected retrospectively from the ICU of Dr. Sardjito Hospital between the 1st of January 2020 and the 31st of December 2020. The study received ethical clearance from the Medical and Health Research Ethics Committee of Universitas Gadjah Mada, Yogyakarta, Indonesia (ethical clearance no. KE/FK/1165/EC; October, 26th 2021).

Study Subjects

The subjects consist of all patients treated in the ICU at Dr. Sardjito Hospital. Samples were determined by using non-probability sampling. This study's population consists of patients who were treated in the ICU of Dr. Sardjito from the 1st of January 2020 to the 31st

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of December 2020. The target population was non-covid patients from the general ICU population from the MICU and SICU during the pandemic. This study did not include other care units, such as the PICU, ICU post-heart surgery, HCU, burn unit, and COVID-19 intensive isolation room. The analysis was conducted separately for surgical, medical, and all ICU patients. The data analyzed and calculated in this study have met the pre-determined inclusion and exclusion criteria. The criteria are as follows:

Inclusion criteria:

1. The patient was treated in the ICU of Dr. Sardjito Hospital.
2. The patient's data is complete.
3. The patient is above 18 years old.
4. Patients were transferred from other ICU hospitals or were readmitted from other in-hospital units.

Exclusion criteria:

1. Patients were admitted after cardiac surgery operations.
2. Variable data loss of more than three or cannot be calculated by the APACHE IV model.

Result Analysis

The study's data analysis focuses on validating the APACHE IV score by assessing its calibration and discrimination abilities. To evaluate discrimination power, the ROC that produces an area under the curve (AUC) with 95% confidence intervals (CIs) was used. A ROC is considered 'good' if it is > 0.80. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration of the APACHE IV score, and a p-value of >0.05 is regarded as a good calibration. The data analysis was conducted using SPSS and included a descriptive analysis.

RESULT AND DISCUSSION

Patient Characteristics

The original data comprised 353 data from all ICU patients, of which 14 were excluded from the study as they did not meet the inclusion criteria. An additional three patients' data were also excluded due to data loss. Thus, this study included and analysed data from 336 ICU patients with 40 variables per patient.

Table 1. The Demographic Data of ICU patients

Variables	N (%)
Gender	
Male	167 (49.7)
Female	169 (50.3)
Age	
<=20	12 (3.6)
21-40	91 (27.1)
41-60	137 (40.8)
61-80	90 (26.8)
>=81	6 (1.8)
Average age	49.65 ± 16.17
Diagnosis	
Medical	149 (44.34)
Surgical	187 (55.65)
Mortality	
Alive	232 (69.04)
Dead	104 (30.95)
APACHE IV Score	
<40	69 (20.53)
41-60	92 (27.38)
61-80	96 (28.57)
81-100	46 (13.69)
>100	33 (9.82)
Total	336 (100)
Average Score	64.27 ± 27.35

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For the age variable, most patients were 41-60 years old, with a total of 137 patients (40.7%). This indicates that middle-aged men mainly populate the date, while extreme ages below 20 and over 80 are small in comparison. Next, the median and mean are 50 and 49.65 ± 16.17, respectively, younger than the average age of the original APACHE IV publication, which is 61.45 ± 0.08 years old. The sample has 169 females (50.3%) and 167 males (49.7), indicating no significant difference in numbers for the gender variable. Next, 149 patients (44.3%) were categorized as medical patients and 187 (55.7%) were labeled as surgical patients. This shows that the data has more surgical patients than medical ones, which is inverse to the original publication of APACHE IV, where medical patients (69.2%) are more abundant than medical ones (30.8%). Moreover, the mortality percentage in this study reached 30.95%, while other similar studies in the same location have lower mortality rates, such as 25.4% (9) and 25.4% (10). In addition, the original publication had a 13.5% mortality rate. In Table 2, we can see that the distribution of the APACHE score is 64.27. This number is higher than the original publication, where the average APACHE score was 46.43. Patients tend to aggregate in scores 41-80 covering 55.96% of the study population.

Based on Table 2, 69 patients with an APACHE score of less than 40 survived, 97.1% of all cases. Conversely, patients with APACHE scores of more than 100 had a higher mortality rate, with 63.6% of patient cases resulting in death. These results suggest that a higher score is proportional to increased patient mortality, even though with a score >100, the outcome of death is less likely than the previous score range of 81-100, which has a 73.9% mortality rate.

Next, as we have found a discrepancy, a chi-square test was conducted to determine the fault and significance of the mortality proportion between patients with APACHE IV scores higher than 100 and below 100. The p-value for all cases and surgical was significant. However, the p-value for medical cases was not significant.

Table 2 also shows the patients' distribution based on their referred case and acquired APACHE score. The surgical category has more patients that aggregate into the lower score categories. Meanwhile, the medical category is more distributed on the middle side while having more cases with high scores compared to the surgical category. Surgical patients also tend to have better survivability outcomes, with 86.1% of their patients surviving the ICU. Conversely,

Table 2. Patient Data Distribution Based on Patient Case, Mortality, and APACHE IV Score

	APACHE IV Score					Chi-Square
	<40	**41-60**	**61-80**	**81-100**	**>100**	**P Value****
All Cases (n)	69	92	96	46	33	
Death (n; %)	2 (2.9%)	14 (15.2%)	33 (34.4%)	34 (71.7%)	21 (63.6%)	0.00*
Average Score: 64.27+-27.35						
Surgical (n)	61	67	38	14	7	
Death (n; %)	0 (0%)	6 (8.5%)	7 (18.4%)	10 (71.4%)	3 (42.8%)	0.024*
Average Score: 52.86+-22.80						
Medical (n)	8	25	58	32	26	
Death (n; %)	2 (25%)	8 (32%)	26 (44.8%)	24 (75%)	18 (69.2%)	0.058
Average Score: 78.59+-25.99						

*p-value is significant; p<0.05
**Chi-square P value for mortality comparison between patients with scores above 100 and scores below 100.

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medical patients are less likely to survive with 52.3% of treated patients resulted in death.

Model Validity Test
Discrimination

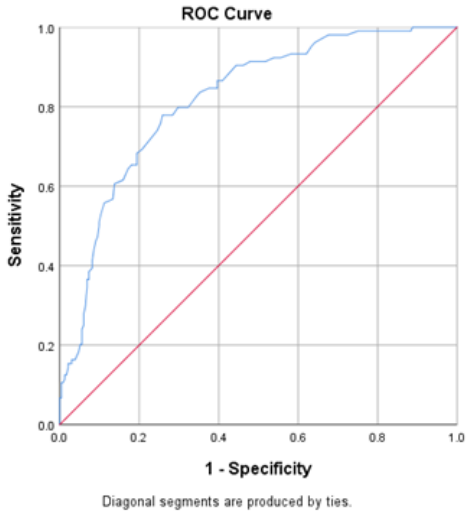

Figure 1. ROC Curve All Cases (AUC = 0.819 [0.772-0.866]; 95%CI)

Figure 1 shows the discrimination result of the APACHE IV score for mortality. The area under the curve (AUC) of the Receiver Operating Characteristics (ROC) has a 95% confidence interval (CI) for mortality at 0.819 (0.772-0.866). This result indicates that the discriminative power in predicting mortality is strong in all cases. Next, the cut-off point for the mortality prediction is 67.5, with a sensitivity of 77.9% and specificity of 74.1%. This suggests that patients with APACHE IV scores above this cut-off point will be more likely to receive a death outcome and treatments, for these kinds of patients must be handled with more caution.

Figure 2 shows the discrimination of the APACHE IV score for mortality in medical cases; the area under the curve (AUC) of Receiver Operating Characteristics (ROC) with a 95% confidence interval (CI) for mortality is 0.698 (0.614-0.782). This discrimination power is considered weak. Figure 3 exhibits the discrimination of the APACHE IV score for mortality surgical cases; the area under the curve (AUC) of Receiver Operating Characteristics (ROC) with a 95% confidence interval (CI) for mortality is 0.848 (0.776-0.921). This discrimination power is strong.

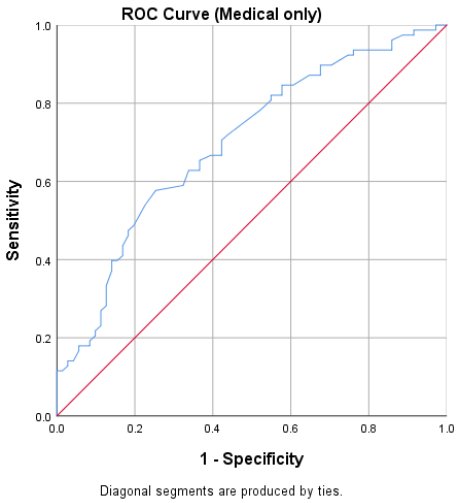

Figure 2. Medical cases (AUC = 0.698 [0.614-0.782]; 95% CI)

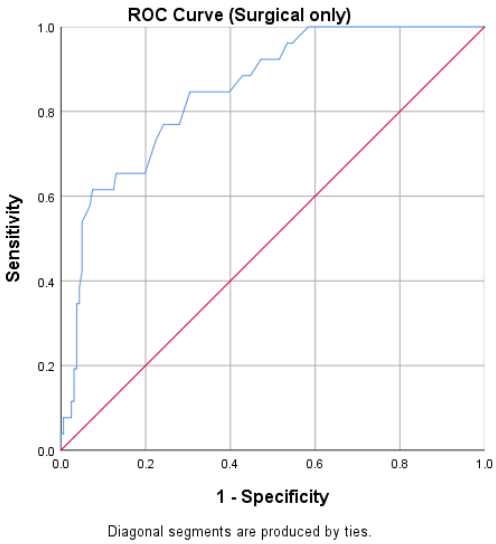

Figure 3. Surgical cases (AUC = 0.848 [0.776-0.921]

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Calibration

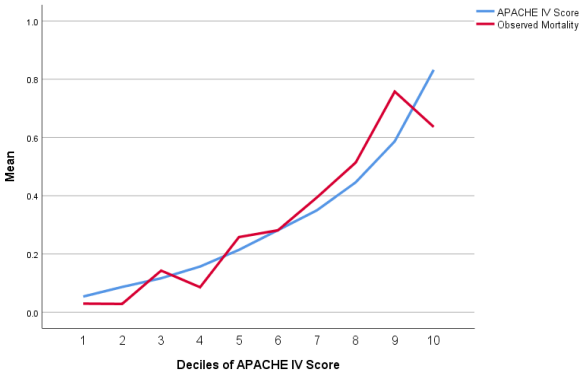

Figure 4. All cases (p = 0.023)

Figure 5. Medical case (p = 0.569)

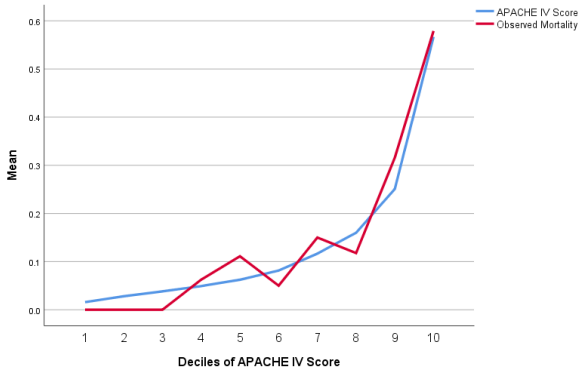

Figure 6. Surgical case (p = 0.579)

In all cases, the APACHE IV model showed poor calibration (p<0.05) for mortality prediction. The APACHE score prediction is similar to the observed mortality in the low-risk but underestimated in the high-risk. However, the performance of the APACHE IV varies based on the case. Medical and surgical cases showed good calibration (p>0.05) for mortality prediction. The APACHE score slightly underestimated the mortality in medical cases, as shown in Figure 5. For surgical cases, the APACHE score mortality prediction varies. However, overall, the mortality prediction for surgical cases was similar to the observed mortality, as shown in Figure 6.

The study shows that the APACHE IV score gives good determination (AUC = 0.819 [0.772-0.866]; 95%CI) in predicting mortality in all cases, including during the pandemic. Although the discrimination is not as good as in the original population study, the quality of discrimination is still considered strong. This is also proven by various studies (7–9) on the Indonesian population before the pandemic (10). However, the discrimination quality in surgical and medical cases resulted in different values. Patients in the surgical cases have good discrimination (AUC = 0.848 [0.776-0.921]; 95% CI), whereas patients included in the medical cases showed weak discrimination power (AUC = 0.698 [0.614-0.782]; 95% CI).

The calibration using the Hosmer-Lemeshow shows that the APACHE IV score has poor performance in predicting mortality (X2 = 17.722, p = 0.023). From the calibration curve, the model prediction appeared to fit in the first four deciles. However, there are prediction inaccuracies starting from the fourth decile onwards, where the prediction starts to underestimate the mortality. Nevertheless, calibration tests done separately on surgical and medical populations produced different results. The p-values were 0.569 for medical and 0.579 for surgical cases, which means both show good calibration in predicting mortality. Additionally, a study in Malaysia (9) showed that the APACHE IV also has poor calibration (p<0.0001). A study in Korea (8) retrospectively tested the APACHE IV, APACHE II, and SAPS 3 scores in a Korean ICU and found that all models show good discrimination (0.80, 0.85, and 0.86, respectively) but poor calibration for all models

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($p<0.05$). The same study also showed that different subgroups of admission types and admission diagnoses might produce different calibration results, such as patients with stomach cancer surgery having good calibration ($p>0.05$), but poor calibration is seen in other surgeries (8).

This study was conducted on patient samples obtained during the 2020 pandemic. After going through the inclusion and exclusion criteria, 336 samples out of 353 were used for this study. The number of patients who died in this study with an APACHE IV score above 100 was 63.6%, whereas, in the original research, it accounts for 47%. In this study, the number of patients who died with APACHE IV scores over 100 was smaller compared to patients with scores of 81-100. This is proven insignificant, especially for patients in medical cases, as people with scores above 100 should have higher mortality rates than those with lower APACHE IV scores. These findings may affect the discrimination or calibration of the APACHE IV validation, as mortality in patients with scores above 100 may not represent the real cases.

Compared to other studies, they only assess the mortality prediction without including the PLOS prediction. Most studies also used more than one parameter other than the APACHE IV score for their comparison (7,11,12). Research in Iran (7) found that the APACHE IV has good discrimination but poor calibration for mortality prediction (AUC = 0.81; p = 0.036). Additionally, a study comparing different risk prediction model validity found that APACHE IV has the best discrimination and calibration (AUC = 0.745; p = 0.541) for mortality prediction if compared to other predictors such as APACHE II, SAPS 3, and MPM0 III (11). Another recent research done during the pandemic compared the accuracy of the APACHE IV score to the APACHE II and Sequential Organ Failure Assessment (SOFA) scores for mortality in patients with Coronavirus disease in the ICU. The study revealed that all scores had poor discrimination on the general population (APACHE IV 0.67 vs. APACHE II 0.63 vs. SOFA score 0.53) (13).

The APACHE IV has good discrimination but lacks calibration in predicting mortality. Different outcomes may result from variations in patient characteristics, clinical practice, assurance, quality, and services provided by healthcare systems. One of the key points in this study is that the patient population is taken from a pandemic setting. In this pandemic condition, changes in case mix and illness severity have been noted (6,14), and these changes may have impacted the predictive accuracy of risk factors. As quoted, “Calibration may weaken over time, especially due to the effects of altered patient interventions and case-mix.” (7). The accuracy of prognosis prediction was impacted by differences between clinical practices between the USA and Indonesia, case-mix differences, insurance policies, step-down policies, and hospital policies relating to patients' end-of-life status.

Moreover, medical resource management was challenged during the pandemic, as a big part of the medical resources was dispatched to handle the COVID-19 pandemic, leading to other departments being forced to adapt to the situation (12). Additionally, the lack of hospital preparedness in the early stages of the pandemic also contributes to the hospital’s service quality to patients, leading to patient safety problems, such as delayed treatment for patients (15). These conditions may affect the predictive accuracy of these models as the changing service quality may lead to different outcomes.

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Prognostic models have the potential to improve the standard of critical care in Indonesia. In the long run, medical practitioners will benefit from using a good prognostic model as a clinical decision-support tool.

CONCLUSION

APACHE IV showed good discrimination (AUC 0.819) but poor calibration in predicting mortality ($p<0.05$). APACHE IV also has good discrimination in predicting mortality for patients in surgical cases but has poor discrimination in medical cases. Both medical and surgical have good calibration ($p>0.05$).

STRENGTH AND LIMITATIONS

There are several limitations to this study. First, some parameters were absent in some patients, which may affect the end prediction scores. Second, only a year's worth of data was collected, whereas longer and more data sets might yield different results, this happened because we wanted to study the population with a case mix, which comprised ICU patients admitted during the Pandemic. Therefore, the time could not be extended for more than this one year.

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Conflict of Interest

The authors declared there is no conflict of interest in this study.

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Authors' Contributors

All authors have contributed to all processes in this research.

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Case Series

OPIOID-FREE ANESTHESIA IN OPHTHALMIC SURGERIES

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ABSTRACT

Introduction: Opioid-free anesthesia (OFA) is an alternative to Opioid based anesthesia (OBA) which uses multimodal analgesia to replace opioids. However, its feasibility, safety, and exact recommended combination remain debatable. **Case Series**: We administered OFA in 5 types of elective ophthalmic surgeries under general anesthesia in ASA 1-2 adult patients (evisceration, ocular exenteration, periosteal graft, scleral buckling, vitrectomy, and dacryocystorhinostomy) to assess the feasibility of OFA. We gave preoperative Paracetamol and Pregabalin with Dexmedetomidine as a loading dose (1 mcg/kg in 10 minutes) and maintenance at 0.7 mcg kg^{-1} per hour. Induction was performed using Propofol 1-2 mg kg^{-1}, Lidocaine 1-1.5 mg kg^{-1} IV, and Rocuronium. Before the incision, Dexamethasone and Ranitidine were given. Maintenance was done using Dexmedetomidine and Sevoflurane. Fentanyl was used as rescue analgesia if required. Dexmedetomidine was stopped 15-30 minutes before the procedure ended. Metoclopramide and Ketorolac were given as postoperative management. Throughout the procedure, our patients had stable hemodynamics, did not experience life-threatening bradycardia, and did not require rescue analgesia. All patients regained full consciousness and did not experience postoperative nausea and vomiting, emergency delirium, or coughing. **Conclusion:** Multimodal analgesia was an excellent intraoperative OFA regimen as an alternative to OBA and provided controlled hypotension in ocular surgery. Safe OFA is possible with combined analgesia regimens, strict intraoperative monitoring, and adequate anesthesia depth.

Keywords: Feasibility; Ophthalmic surgery; Opioid-free anesthesia; Multimodal analgesia; Safety

ABSTRAK

Pendahuluan: *Opioid free anesthesia (OFA)* merupakan alternatif untuk *opioid based anesthesia (OBA)* menggunakan analgesia multimodal untuk menggantikan opioid. Kelayakan, keamanan dan kombinasi tepat yang dianjurkan masih menjadi perdebatan. **Serial kasus:** Kami menggunakan OFA dalam 5 jenis operasi mata elektif dengan anestesi umum pada pasien dewasa ASA 1-2 (eviscerats, eksenterasi okular, cangkok periosteal, buckling scleral dan vitrektomi serta dakriosistorhinostomi) untuk menilai kelayakan OFA. Pemberian parasetamol dan pregabalin pra operasi dengan dexmedetomidine, diberikan sebagai dosis muatan (1mcg/kg dalam 10 menit) dan dosis pemeliharaan 0,7 mcg/kg^{-1}per jam. Induksi dilakukan dengan propofol 1-2 mg/kg^{-1}per jam, lidokain 1-1.5mg/ kg^{-1}per jam, dan rocuronium. Sebelum insisi, akan diberikan deksametason dan ranitidine. Pemeliharaan dilakukan dengan menggunakan dexmedetomidine dan sevoflurane. Jika diperlukan fentanyl akan diberikan untuk membantu obat analgesia utama. Dexmedetomidiin akan dihentikan 15-30 menit sebelum prosedur berakhir. Metoclorperamide dan ketorolac diberikan sebagai manajemen pasca operasi. Selama prosedur berlangsung, hemodinamik pasien dalam keadaan stabil, tanpa bradikardia, dan tidak memerlukan analgesia tambahan. Pasca operasi semua pasien kembali sadar, tidak mengalami gejala mual dan muntah, penurunan kesadaran , maupun batuk. **Kesimpulan:** Analgesia multimodal bekerja sebagai rejimen OFA intraoperatif yang sangat baik dan memberikan alternatif untuk OBA, dan memberikan hipotensi terkontrol pada operasi mata. Regimen kombinasi analgesia, pemantauan intraoperatif yang ketat, dan kedalaman anestesi yang adekuat dapat mencapai keamanan prosedur OFA.

Kata kunci: Kelayakan; Operasi mata; *Opioid-free anesthesia*; Analgesia multimodal; Keselamatan

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INTRODUCTION

Opioid-free anesthesia has been gaining popularity in recent years. However, debates regarding the safety of opioid-free regimens have been the center for discussion, with trials showing increased risk for bradycardia and hypotension, likely due to the use of Dexmedetomidine (DEX) as a replacement for opioid agents such as remifentanil (1). The added benefits of an opioid-free regimen include a lower incidence of postoperative nausea and vomiting, reduced incidence of delirium, and lower incidence of hyperalgesia.

DEX is an alpha agonist commonly used for the controlled hypotension (2) technique in maxillofacial, ear, nose, and throat, as well as ocular surgery. With this in mind, we administered opioid-free anesthesia (OFA) in 5 elective ophthalmic surgery patients with Dex to evaluate the feasibility of OFA in this population (3). We gave a standardized regiment using 1 gram of oral paracetamol (PCT) and 75 mg Pregabalin (PGB), given 2 hours before surgery, DEX (1 mcg kg^{-1} in 10 minutes, followed by 0.7 mcg kg^{-1} per hour), Lidocaine (LD) IV 1-1.5 mg kg^{-1}, and Ketorolac 30 mg IV for postoperative analgesia (3,4). All patients were given Propofol 1-2 mg kg^{-1}, Sevoflurane (SEV) 1 MAC, and Rocuronium 0.4 mg kg^{-1} for induction. Baseline heart rate and blood pressure were monitored closely throughout the protocol at seven distinct time points; before starting Dexmedetomidine (T0), before induction (T1), after the insertion of the airway device and induction (T2), following incision (T3), before stopping Dexmedetomidine (T4), at the end of the procedure (T5), and the recovery room (T6). Rescue analgesia (Fentanyl 50 mcg) was administered if there was an increase in heart rate or blood pressure of over 20% of the baseline.

CASE SERIES

Case 1: Ocular evisceration and dermofat graft from the abdomen

A 25-year-old male was referred to our hospital due to a periosteal cyst and retinal detachment of the right eye. The ophthalmology department planned to eviscerate the right eye to maintain globe integrity. The patient was assessed by the American Society of Anesthesiologists (ASA) 1 and had no airway difficulties. Two hours before surgery, he was given paracetamol and pregabalin. Upon arrival at the operating theater (OT), he was placed on standard ASA monitoring tools, and his baseline values were recorded. Induction was performed following preoxygenation using Lidocaine 1.5 mg kg^{-1} IV bolus, Propofol 1-2 mg given as titrated dosing, SEV at 1 MAC, and muscle relaxation was achieved using 0.4 mg kg^{-1} Rocuronium. A supraglottic airway device (LMA, Unique) was inserted. During draping, the patient was given Ranitidine 50 mg and Dexamethasone (DEXA) 5 mg IV bolus. SEV was increased to 1.1-1.2 MAC and was maintained throughout the procedure. Dexmedetomidine was stopped 15 minutes before the procedure ended while maintaining SEV at 1 MAC. Ketorolac 30 mg and Metoclopramide 10 mg were given 15 minutes before the procedure ended.

The SGA was removed while the patient was deeply anesthetized while maintaining spontaneous breathing. The patient had a stable range of vital signs throughout the procedure (68 minutes), with heart rate and blood pressure variations falling within 20% of the baseline. The anesthesia duration was 90 minutes. The patient experienced bradycardia but was still within a tolerable range (>50 beats per minute). He did not experience any desaturation throughout and after the procedure. After 15 minutes in the

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recovery room (RR), he regained full consciousness with a Numerical Rating Scale (NRS) of 0-1. There was no PONV, coughing, delirium, or desaturation.

Case 2: Mass exenteration of the left eye

A 32-year-old male was referred to our center due to invasive intraocular squamous cell carcinoma extending to the superior-lateral-inferior rectus and left lacrimal gland. He was scheduled for mass exenteration of the left eye. The patient was assessed with ASA 2 and had no airway difficulties. Similarly, he was given PCT and PGB preoperatively and was placed on standard ASA monitoring. He was administered DEX 10 minutes before induction. Induction was performed using a combination of LD, Propofol, and Rocuronium while maintaining DEX at 0.7 mcg/kg/hour. This patient had a baseline heart rate of 100-110 bpm, possibly due to the tumor, and was unresponsive to fluid challenge. Upon insertion of LMA and incision, there were no significant changes to the heart rate and blood pressure. His heart rate gradually decreased following mass exenteration, further supporting our initial hypothesis. Dexmedetomidine was stopped 30 minutes before the procedure's completion, and ketorolac was administered 15 minutes before the procedure ended. Sevoflurane was stopped upon procedural completion. The patient recovered spontaneous breathing after 15 minutes and was fully awake 25 minutes after his transfer to the RR. Similarly, there was no PONV, coughing, delirium, or desaturation.

Case 3: Periosteal graft of the left eye

A 33-year-old female was scheduled for a periosteal graft due to left ocular perforation caused by a corneal ulcer. She was assessed with ASA 2, with leukocytosis 12,170, and had no airway difficulties. She had experienced constant ocular pain of NRS 1-2, controlled with routine PCT (3x1 gram). Similar to previous cases, she was administered PGB and an extra dose of PCT preoperatively. She had an NRS of 0-1 when she reached the OT. She was started on Dexmedetomidine for 10 minutes before induction. Induction was performed using lidocaine, propofol, and rocuronium. Upon insertion of the LMA and incision, there was no significant increase in pulse or blood pressure. The intraoperative patient was stable. The procedure was completed after 45 minutes, and anesthesia was administered for 80 minutes. DEX was stopped 30 minutes before the procedure ended, while SEV was decreased to 1 MAC and was stopped 15 minutes before the procedure's completion. As we had experienced a delayed return of spontaneous breathing, we started giving assisted manual ventilation to trigger spontaneous breathing 15 minutes prior. The patient recovered spontaneous breathing 5 minutes after the procedure's completion and was transferred to the RR. She regained consciousness after 30 minutes. There was no PONV, coughing, delirium, or desaturation.

Case 4: Scleral buckling, vitrectomy, endolaser, and silicone oil insertion of the right eye

A 22-year-old female experienced retinal detachment of the right eye with proliferative vitreoretinopathy. She was scheduled for scleral buckling, vitrectomy endolaser, and silicone oil insertion of the right eye. She was assessed with ASA 2, with nodular opacity in her chest x-ray. Clinically she did not experience dyspnea or tachypnea and had no signs of increased work of breathing, cough/fever, and airway difficulties. She was given PCT, PGB, and DEX for 10 minutes

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before induction. Induction was performed with Propofol, LD, Rocuronium, and SEV. LMA was inserted. Before the incision, she was given Dexamethasone and Ranitidine. Throughout the procedure, she had stable hemodynamics. Oculocardiac reflex (OCR) occurred twice throughout the procedure but did not confer hemodynamic instability. The operator was asked to pause until the heart rate recovered before resuming the procedure. The procedure was completed after 150 minutes, and the anesthesia duration was 180 minutes. DEX was stopped 20 minutes before the procedure ended. The patient recovered spontaneous breathing 10 minutes after the procedure ended. Following the deep removal of the airway device, she was transferred to the RR. She regained full consciousness without PONV, delirium, desaturation, bradycardia, or coughing. She had a well-controlled pain score of 0-1.

Case 5: External dacryocystorhinostomy of the left eye

A 43-year-old female was admitted to our center due to nasolacrimal duct obstruction. She was planned for an external dacryocystorhinostomy. She was assessed with ASA 2, with controlled diabetes mellitus on Metformin 3x500 mg, and had no airway difficulties. We administered general anesthesia with endotracheal intubation with the previously described opioid-free regiment and a combination of PCT, PGB, DEX, LD, propofol, SEV, and Rocuronium. However, we did not give Dexamethasone to this patient. Following intubation, the patient's vital signs remained stable and smooth intubation was performed without using Fentanyl. Intraoperative, the patient maintained stable vital signs. DEX was stopped 30 minutes before the end of the procedure. The procedure was completed after 85 minutes, and the anesthesia duration was 120 minutes. She recovered adequate spontaneous breathing 5 minutes after the procedure ended and was transferred to the RR, where she regained consciousness. There was no PONV, coughing, or delirium, with adequate analgesia (NRS 0-1).

Table 1. Doses and Agents Used During the Procedure

Case No (Body weight)	2 hours prior		10 minutes prior	Induction					Before incision			Before procedure ends (dose in mg)		Airway device
	Pct (mg)	Pregabalin (mg)	Dex (mcg)	Lidocaine (mg)	Propofol (mg)	Sev (MAC)	Dex (mcg/hour)	Rocuronium (mg)	Dexa (mg)	Ranitidine (mg)	Sev (MAC)	Ketorolac (mg)	Metoclopramide (mg)	
Case 1 (50 kg)	1000	75	50	60	100	1	35.0	50	5	50	1.2	30	10	LMA
Case 2 (55 kg)	1000	75	50	60	100	1	38.5	30	5	50	1.2	30	10	LMA
Case 3 (72 kg)	1000	75	70	80	100	1	50	20	5	50	1.2	30	10	LMA
Case 4 (54 kg)	1000	75	54	60	100	1	37.8	20	5	50	1.1	30	10	LMA
Case 5 (52 kg)	1000	75	52	80	100	1	36.4	20	5	50	1.1	30	10	ETT

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Table 2. Changes in Vital Signs During the Procedure

Case Number	Parameters	Time points						
		T0	T1	T2	T3	T4	T5	T6
Case 1	Heart rate (beat per minute)	82	62	60	72	70	62	58
	Blood pressure (mmHg)	132/83	116/68	94/58	105/66	110/71	101/72	97/62
	Respiratory Rate (times per minute)	16	18	NA	NA	NA	18	18
	Peripheral Oxygen Saturation (%)	99%	99%	99%	99%	99%	99%	99%
	Numeric Rating Scale	1	1	NA	NA	NA	NA	0-1
Case 2	Heart rate (beat per minute)	88	104	100	110	90	80	75
	Blood pressure (mmHg)	132/78	120/67	94/63	109/77	100/58	102/57	98/64
	Respiratory Rate (times per minute)	18	18	NA	NA	NA	18	18
	Peripheral Oxygen Saturation (%)	99%	99%	99%	99%	99%	99%	99%
	Numeric Rating Scale	1-2	1	NA	NA	NA	NA	0-1
Case 3	Heart rate (beat per minute)	91	88	80	82	81	78	74
	Blood pressure (mmHg)	141/100	120/79	115/71	128/79	130/80	118/78	116/70
	Respiratory Rate (times per minute)	18	18	NA	NA	NA	18	18
	Peripheral Oxygen Saturation (%)	99%	99%	99%	99%	99%	99%	99%
	Numeric Rating Scale	0-1	0-1	NA	NA	NA	NA	0-1
Case 4	Heart rate (beat per minute)	92	75	79	72	78	76	81
	Blood pressure (mmHg)	130/75	127/77	87/57	93/62	84/50	98/57	106/64
	Respiratory Rate (times per minute)	18	18	NA	NA	NA	18	18
	Peripheral Oxygen Saturation (%)	98%	99%	99%	99%	99%	99%	99%
	Numeric Rating Scale	0	0	NA	NA	NA	NA	0
Case 5	Heart rate (beat per minute)	80	78	72	68	69	61	76
	Blood pressure (mmHg)	125/80	130/81	110/72	112/64	104/60	100/58	118/71
	Respiratory Rate (times per minute)	18	18	NA	NA	NA	18	16
	Peripheral Oxygen Saturation (%)	99%	99%	99%	99%	99%	99%	99%
	Numeric Rating Scale	1	1	NA	NA	NA	NA	0-1

DISCUSSION

To our knowledge, this is the first case series that evaluated the feasibility of opioid-free anesthesia in different types of ocular surgeries. In this series, we showed that opioid-free anesthesia is possible and beneficial in a wide range of ocular surgeries through LMA or even intubation.

We used a combined regiment of preemptive analgesia with oral paracetamol and pregabalin 2 hours before the procedure. This provided sufficient time to hit plasma level (1) and ensured hydration. The use of intravenous lidocaine and Dexmedetomidine allows for sufficient analgesia and sympathetic blunting throughout the surgery. We did not use topical lidocaine as patients were sedated with Dexmedetomidine before induction. Nonetheless, using IV lidocaine 1-1.5 mg bolus and Dexmedetomidine confer analgesia during the administration of propofol and insertion of airway device and surgical incision. The sedative nature of Dexmedetomidine gave anti-anxiolytic properties before induction and reduced the need for propofol during induction (2).

The use of Dexmedetomidine brings the added benefit of controlled hypotension, which is preferable in ocular surgery. Controlled hypotension also provided optimal visualization of the operating field and resulted in less bleeding. Intraoperative, the patients had stable hemodynamics, which indicates an added benefit of stable intraocular pressure. Controlled hypotension is easily reversed with Dexmedetomidine, bringing adequate surgeon satisfaction and excellent procedural efficiency.

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There were concerns about bradycardia and desaturation following the use of Dexmedetomidine. However, we anticipated this pulse reduction and thus selected patients with a baseline heart rate of > 70 bpm and systolic blood pressure of > 100 mmHg. We also screened possible candidates to be < 55 years of age without any cardiac problems. Some patients experienced stable bradycardia without significant changes to blood pressure or saturation. None of these cases had bradycardia < 40 bpm, even in procedures with a high oculocardiac reflex (OCR) risk. Dexmedetomidine was associated with less emergence agitation and post-operative vomiting without increasing the incidence of OCR (3). We did not experience severe OCR that requires rescue atropine as they were easily managed by stopping the stimulus. In all patients, there was no emergence of delirium or PONV.

Close intraoperative monitoring allows for rapid management of any hemodynamic instability. However, in our cases, we found little changes to the heart rate, blood pressure, and oxygen saturation throughout the procedure. We postulated that the combined use of Dexmedetomidine, propofol, and lidocaine reached the deep anesthesia plane enough to ameliorate possible sympathetic response to nociception during incision. The combined Dexmedetomidine and Sevoflurane 1.1-1.2 MAC could maintain deep anesthesia and blunts nociception-induced responses (4,5).

We also found that we could use less Rocuronium for these patients, as little as 0.4 mg/kg for procedures lasting for 1-2 hours. The return of spontaneous breathing was slower in these cases, which contributed to the increased time for LMA removal. The use of Dexmedetomidine was associated with an increased duration of action of Rocuronium in Sevoflurane anesthesia (6,7). However, this disadvantage can be easily solved with the use of sugammadex. In our center, the use of sugammadex is expensive and is not the standard regimen for general anesthesia. Thus, we used neostigmine, an acetylcholine esterase inhibitor, for the reversal. We also observed that our use of atropine for the reversal regimen did not confer significant tachycardia in our patients. Adequate breathing was achieved in all cases.

Despite the use of Sevoflurane (MAC 1-1.2), we had zero cases of PONV, agitation, or coughing. This is beneficial in patients with ocular surgery as these adverse effects might lead to increased intraocular pressure and possible dislodging of the implant (8–10). We did not use Ondansetron or Propofol at the end of the procedure.

CONCLUSION

Safe opioid-free anesthesia in ophthalmic surgery is possible with careful patient selection and close intraoperative monitoring. The added benefits of opioid-free anesthesia include less PONV, coughing, and emergency delirium. The use of Dexmedetomidine allows the use of controlled hypotension while maintaining stable hemodynamics.

LIMITATIONS OF THE STUDY

The main limitation of this study is the lack of nociceptive monitoring tools, such as Connox or ANI. Thus, the direct relationship between our regiments and the nociceptive index could not be directly assessed. Although the main effect of sympathetic activation due to nociception is rapidly increased heart rate and blood pressure, such observations might be masked using medications such as beta-blockers. Hence, we did not include patients with cardiac comorbidities and arrhythmias.

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Tachycardia can also be caused by a multitude of etiologies, such as hypovolemia and ocular pain. Therefore, we used preoperative analgesia. We also asked the subjects to maintain adequate fluid intake and encouraged fluid intake 2 hours before the procedure by instructing the patients to take the medication orally.

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Conflict of Interest
There is no conflict of interest.

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None

Authors' Contribution
Conception and design of the case series: ART, HA; Informed consent and performed the anesthesia: ART, HA; Interpretation and data analysis: ART, HA, RF; Drafting the manuscript: ART, HA, TC, INT; Final approval of the manuscript: ART, RF

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Case Report

PRILOCAINE 2% FOR SPINAL ANESTHESIA IN INCARCERATED INGUINAL HERNIA SURGERY WITH CONGESTIVE HEART FAILURE

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ABSTRACT

Introduction: Congestive heart failure (CHF) is a disease caused by abnormalities in the myocardium. This abnormality reduces the heart's ability to pump blood throughout the body. Anesthetic drugs have a major cardiovascular effect under general and regional anesthesia. **Objective:** This study aims to examine the effect of prilocaine as a subarachnoid block regional anesthetic drug in patients undergoing non-cardiac surgery with comorbid heart failure. **Case Report:** A 59-year-old man came complained of a lump in his left upper groin that had been present since a day before his admission to the hospital. The lump could not be inserted. The patient felt pain in the lump area with a visual analog score (VAS) of 7-8. His blood pressure was 138/84 mmHg, pulse rate was 104 times per minute, respiration rate was 22 times per minute, temperature was 36ºC for axillary measurement, oxygen saturation was 92% based on room oxygen, and VAS was 7-8. The abdominal examination revealed a lump in the patient's left upper groin that could not be reinserted, hyperemic, and painful when pressed. With an EF Teich of 17.1%, the echocardiographic examination revealed that the dimensions of the patient's heart chambers (RV and LV dilatation) and LV systolic function had decreased. **Conclusion:** Stable hemodynamics in non-cardiac surgery with a relatively short duration is the main choice for HF patients. Spinal anesthesia with a regimen of 2% prilocaine at a dose of 80 mg plus 0.1 mg morphine resulted in stable hemodynamics and low pain scores in patients with comorbid congestive heart failure undergoing non-cardiac surgery.

Keywords: Cardiovascular disorders; Congestive heart failure; Hernia; Prilocaine; Spinal Anesthesia

ABSTRAK

Pendahuluan: Penyakit jantung kongestif (CHF) merupakan penyakit yang disebabkan karena adanya kelainan pada otot miokardium sehingga kemampuan jantung untuk memompa darah ke seluruh tubuh berkurang. Obat – obatan anestesi mayoritas memiliki efek kardiovaskular, baik dalam anestesi umum maupun regional. **Tujuan:** Studi ini bertujuan untuk melihat efek prilokain sebagai obat anastesi regional subarachnoid blok pada pasien yang menjalani operasi non-cardiac dengan komorbid penyakit gagal jantung. **Laporan Kasus:** Seorang laki-laki berusia 59 tahun, datang dengan keluhan muncul benjolan pada lipatan pada kiri sejak 1 hari sebelum masuk rumah sakit, benjolan tidak dapat dimasukkan. Pasien merasa nyeri pada area benjolan dengan nilai visual analog score (VAS) 7-8. Tanda vital menunjukan tekanan darah 138/84 mmHg, nadi 104 kali per menit reguler, respirasi 22 kali per menit, suhu 36o Celcius pengukuran aksila, saturasi oksigen 92% menggunakan oksigen ruangan, dan nilai Visual Analog Scale (VAS) 7-8. Pemeriksaan abdomen didapatkan benjolan pada lipatan paha kiri pasien yang tidak dapat dimasukkan kembali, hiperemis, dan terasa nyeri saat ditekan. Pemeriksaan ekokardiografi pada ditemukan dimensi ruang jantung RV dan LV dilatasi, fungsi sistolik LV menurun dengan EF Teich 17,1%. **Kesimpulan:** Hemodinamik yang stabil pada operasi non-cardiac yang relatif singkat durasinya menjadi pilihan utama untuk pasien HF. Anestesi spinal dengan regimen prilokain 2% dengan dosis 80mg ditambahkan dengan morfin 0,1mg menghasilkan hemodinamik yang stabil dan skor nyeri yang rendah pada pasien dengan komorbid gagal jantung kongestif dalam operasi non-cardiac.

Kata kunci: Gangguan kardiovaskular; Gagal Jantung Kongestif; Hernia; Prilokain; Anestesi Spinal

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INTRODUCTION

Congestive heart failure (CHF) is a disease caused by abnormalities in the myocardium. This abnormality reduces the heart's ability to pump blood throughout the body. CHF is mainly caused by decreased function of the left ventricle. Patients with CHF have a lower ejection fraction (EF) of less than 50% compared to normal patients. In the hospital, CHF patients with serum urea levels >15mmol/L, systolic pressure <115 mmHg, serum creatinine >2.72 mg/dL, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) >986 pg/ mL, and a left ventricular EF < 45% have a high mortality rate (1).

This condition complicates non-cardiac surgeries in CHF patients. Most anesthetic drugs have cardiovascular effects in general and regional anesthesia. Mortality rates during and after surgery for CHF patients increase with the cardiovascular changes often occurring in non-cardiac surgery. A study showed that in CHF patients, the mortality rate reached 8% of the 24,975 patients who underwent surgery (2).

On this occasion, we report the case of a patient with obstructive ileus due to an incarcerated inguinal hernia with comorbid CHF. In this case, the patient must immediately undergo hernioplasty to prevent mortality. Alternative methods and safe anesthetic drugs are needed for these patients to reduce mortality during and after surgery. This report examines the effect of prilocaine as a subarachnoid block regional anesthetic drug in patients with comorbid heart failure undergoing non-cardiac surgery.

CASE REPORT

A 59-year-old man complained of a lump in his left groin that had been present since a day before his hospital admission. The lump could not be inserted. The patient felt pain around the lump. He added that he felt weak, nauseous and vomited more than ten times. However, he did not experience any issues with eating and drinking.

The patient had a history of being hospitalized for having a stroke in 2012. At that time, the patient was hospitalized for nine days. The patient also has a history of diabetes mellitus since 2010. However, the patient rarely takes medication, and in 2019, his diabetes mellitus medication was replaced with insulin, injected once a day. The patient had no history of heart disease, kidney disease, or malignancy. The patient stated that his legs had been swollen frequently since the beginning of 2022. However, the patient never felt short of breath, did not feel tired when walking, and did not feel chest pain.

The patient said that in 2015 he had an operation due to a hernia in the same location. The lump reappeared in the left groin in 2017, but the lump was still able to be reinserted. The patient said the lump came out when he was tired or lifting things.

This patient's initial physical examination in the ward revealed a general state of pain and a Glasgow Coma Score (GCS) of E4V5M6. His blood pressure was 138/84 mmHg, pulse was 104 beats per minute regular, fill and lifting strength, respiration was 22 times per minute for the thoracoabdominal type, his temperature was 36^{o}C for the axillary measurements, oxygen saturation was 92% using room oxygen, and VAS 7-8.

On his neck, the jugular venous pressure (JVP) was 5 + 3 cm H_2O, the trachea did not deviate, and the neck lymph nodes did not enlarge. The thoracic examination, which included an examination of the lungs and heart, revealed crackles in 1/3 of the patient’s right and left lung bases. A cardiac examination

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revealed a shift in the heart boundaries, indicating an enlarged heart.

The abdominal examination showed that the abdominal wall looked flat, and no ascites were seen. Percussion of the tympani occurs in all regions of the abdomen. Furthermore, on palpation, the liver and spleen are not palpable. The lump on the patient's left groin could not be put back, was hyperemic, and painful when pressed. An auscultation examination revealed normal peristalsis with bowel sounds of 10 times per minute.

The examination of the patient's extremities showed no edema in the upper and lower extremities. Acral on all four extremities were warm with a Capillary Refill Time (CRT) of < 2 seconds. He also had a wound on the forefinger of his right toenail.

ADVANCED EXAMINATION

The patient's chest X-ray showed pulmonary edema and cardiomegaly. On the other hand, a plain X-ray of the abdomen revealed a dilated small intestine and possible obstructive ileus (Figure 1).

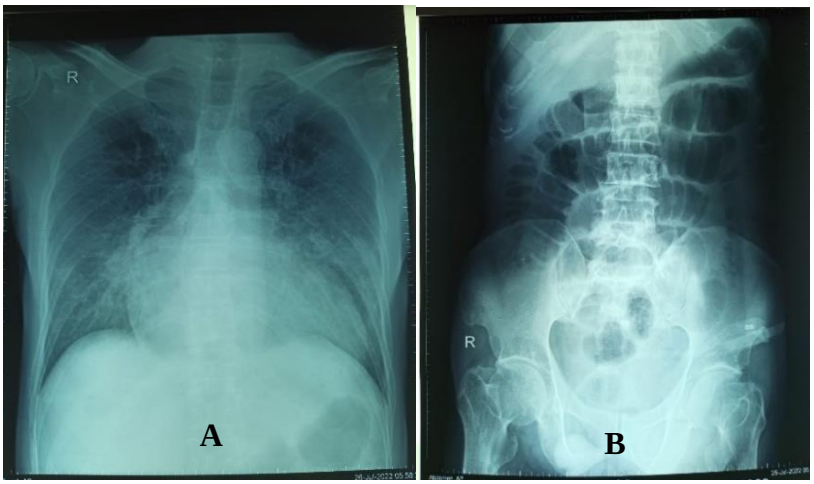

Figure 1. A: Chest X-ray; B: Abdominal X-ray

Table 1. Laboratory Examination

Laboratory Parameter	Result
Hemoglobin	14.9
Platelet	$164x10^3$
Hematocrit	47.9%
Leukocytes	$10.44x10^3$
Sodium	143
Potassium	4.00
Chloride	101
Blood Glucose	88
Creatinine	1.23
SGOT/SGPT	20/10

An echocardiographic examination on July 27, 2022, found that the patient had a dilated RV and LV heart chamber dimensions, decreased LV systolic function with a Teich EF of 17.1%, pseudonormal LV diastolic function, and decreased RV systolic function with a TAPSE of 1.77 cm. The evaluation of the valves revealed mild mitral regurgitation, mild aortic regurgitation, mild tricuspid regurgitation, and trivial pulmonary regurgitation. There was also an eccentric LVH (LVMI = 123.1 g/m2), LASEC (+), LVSEC (+), and an apical-septal thrombus with a diameter of 1.63 x 0.77 cm. Moreover, the IAS was intact, the IVS was intact, and the PDA was negative. There was also pulmonary hypertension with a severe probability, and the laboratory examination showed normal blood test results, as shown in Table 1.

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DIAGNOSIS AND THERAPY

The examination results indicated that the patient was diagnosed with an incarcerated inguinal hernia with congestive heart failure. The patient was scheduled for a hernioplasty with spinal anesthesia. Based on the anamnesis data, a physical examination, a laboratory examination, an ECG, a chest X-ray, and echocardiography, the patient was classified as ASA 3 with NYHA III heart failure. The patient was sitting and identifying the 4th to 5th lumbar intervertebral space at the time of anesthesia. We then performed asepsis and antisepsis. Subsequently, spinal anesthesia was administered using 0.1 mg morphine and 2% prilocaine 80 mg by intrathecal injection. The sensory block was achieved at a height of T10 at 7 min using a pinprick test and cotton swab evaluation. The respiratory muscles were evaluated by asking the patient if there were any complaints regarding ventilation effort and by observing the patient's breathing pattern. Ten minutes after the intrathecal injection of anesthesia was declared effective, the surgery started. The procedure went smoothly for 76 minutes, with relatively stable hemodynamics and respiratory parameters and no vasopressor injection, inotrope, or other analgesia administered (Figure 2).

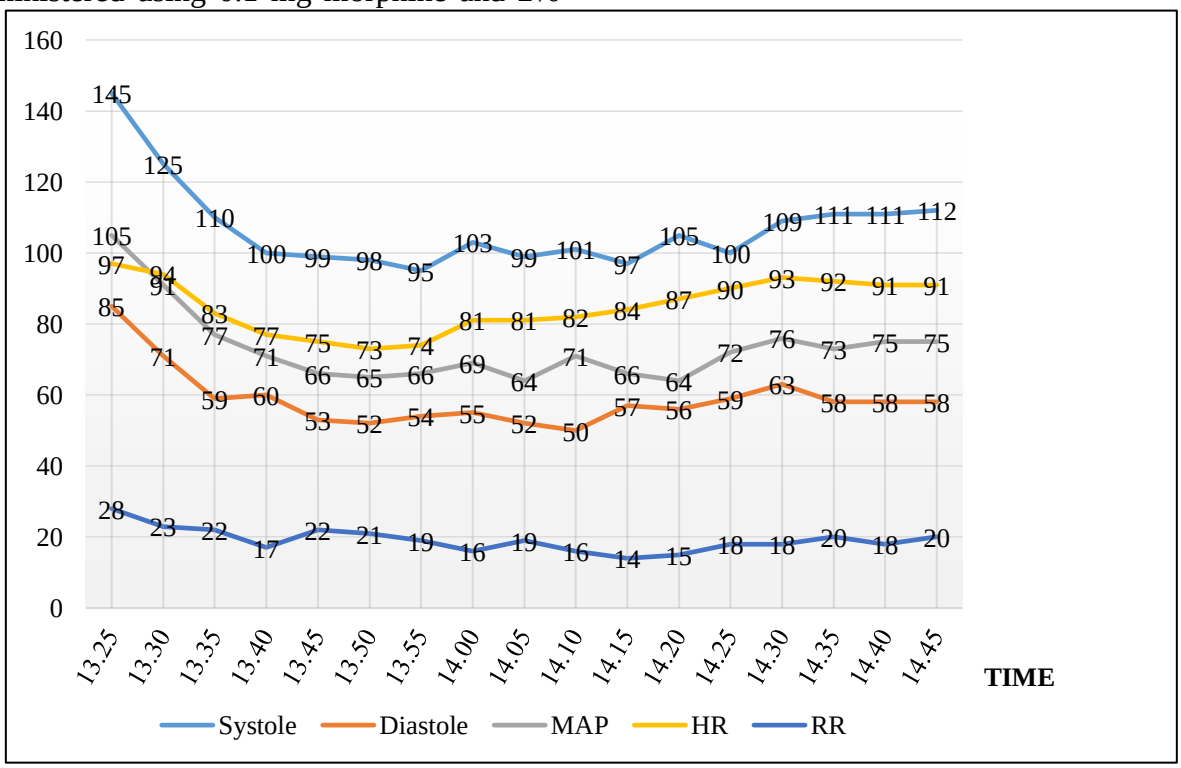

Figure 2. Hemodynamic Parameters During Surgery

After the operation, the patient was transferred to the recovery room and observed. Patient monitoring showed that the patient could move his legs at 15:05, could move the soles of his feet at 15:30, could move his knee at 15:37, and could move his entire leg at 15:40. The patient's hemodynamic and respiratory parameters were relatively stable postoperatively. The patient also had a VAS score of 0 from the beginning of the operation to the end of the postoperative observation (Figure 3). After the motor and sensory blocks had completely disappeared, the patient was mobilized.

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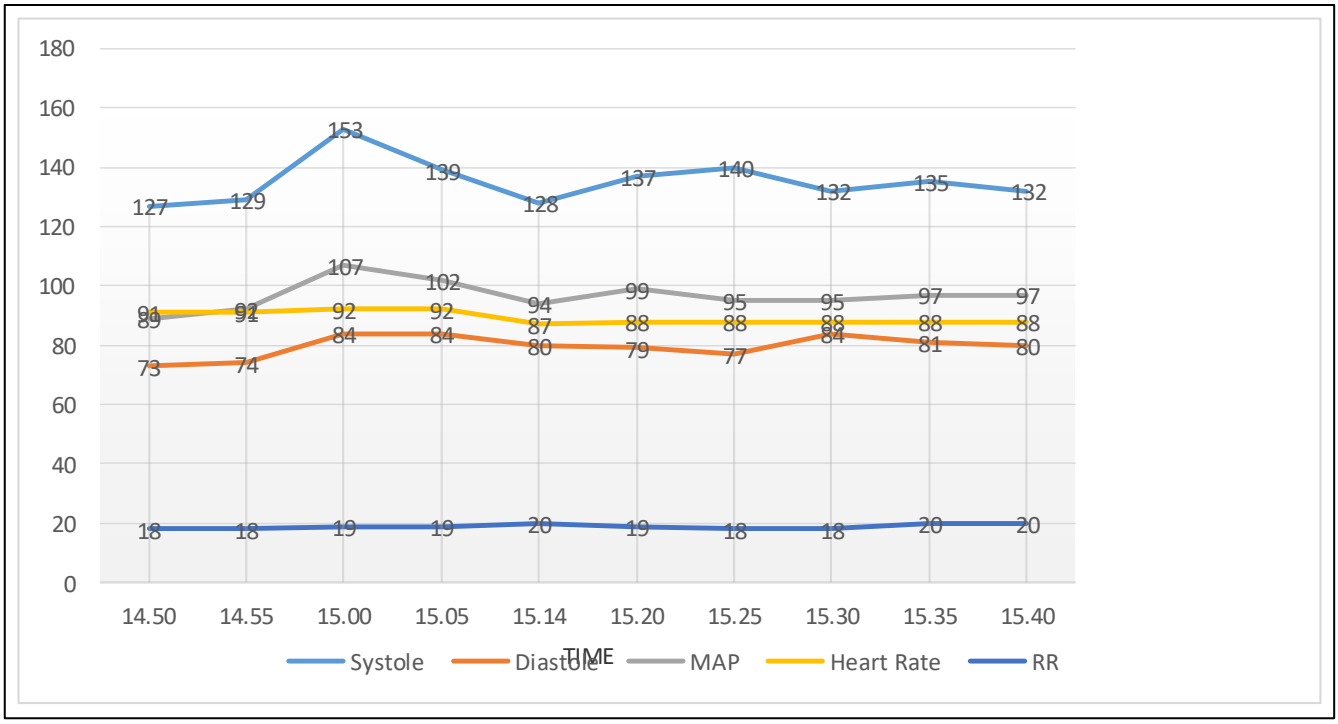

Figure 3. Hemodynamic Parameters After Surgery

DISCUSSION

A hernia occurs when abdominal tissue or organs come out of the abdominal cavity due to a hole caused by congenital abnormalities, weakness, or abdominal wall abnormalities. Based on anatomical location, hernias most commonly occur in the inguinal area (95%). An acute incarcerated hernia is a hernia type that requires immediate surgery (4). The most common complaint in patients with incarcerated hernias is pain. Patients with incarcerated inguinal hernias must undergo surgery as soon as possible to prevent perforation and adhesion of the incarcerated organ (5).

Cardiovascular dysfunction is a disorder that is often found in preoperative patients undergoing both emergency and elective surgery. Patients with weak cardiac ejection fraction pose a challenge for anesthesiologists for anesthesia induction before surgery. Thus, it is necessary to have a complete preoperative plan and preparation. According to the latest reference, the neuraxial block is the best option for patients with low ejection fractions. Meanwhile, spinal anesthesia is the best option for patients with cardiovascular disorders undergoing surgery below the umbilicus. Spinal anesthesia can cause hemodynamic fluctuations in the patient, but the type of drug and the dose used can overcome these problems (3).

Although spinal anesthesia has long been considered a safe anesthetic technique, this does not mean it is without risks or side effects. Hypotension, nausea, and vomiting are some side effects that occur during spinal anesthesia, with an incidence ranging from 7 to 42%. Some other side effects of spinal anesthesia, such as severe bradycardia, cardiac arrest, and dysrhythmias, can also occur during the procedure. However, the incidence of these events is not very high (6).

Postganglionic sympathetic nerves are important in controlling heart function and vascular tone. The most important cardiovascular effects are related to the blockade of vasoconstrictor fibers (below T4),

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resulting in vascular dilatation and inhibition of cardiac sympathetic fibers, leading to decreased chronotropic and inotropic action on the myocardium (T1–5). The spinal anesthetic blocks produce the peripheral sympathetic and splanchnic fiber block but are limited to the mid-thoracic to lumbar regions (T5-L4). This sympathetic block produces vasodilation in the blocked area with compensatory vasoconstriction of blood vessels in the unblocked area. Circulating catecholamines are released from the adrenal medullary system because increased activity in each unblocked fiber in the splanchnic nerve contributes to increased sympathetic activity below and above the blockade level (7).

Bradycardia during spinal anesthesia is caused by two factors: blockade of the sympathetic nerves to the heart muscles and decreased venous return to the heart. Cardiac muscle fibers exit from T1-T4 such that a sympathetic block at the Tl level can completely block sympathetic outflow to the heart. In addition, this degree of sympathetic block during spinal anesthesia is often associated with peripheral vasodilation and decreased preload. In the absence of an adequate venous return to the heart (preload), sympathetic denervation is estimated to result in only a 10% reduction in heart rate from baseline (8).

Prilocaine is a local anesthetic that belongs to the amide class. Prilocaine has moderate potency and a rapid duration and onset of action (9). Several studies reported that prilocaine causes significantly fewer neurologic symptoms than lidocaine or mepivacaine. Ratsch et al. first compared 10% hyperbaric prilocaine to 0.5% hyperbaric bupivacaine. Eighty-eight patients scheduled for lower extremity surgery with a maximum duration of 45 minutes under spinal anesthesia were randomized to receive 15 mg of hyperbaric bupivacaine 0.5% or 60 mg of hyperbaric prilocaine 2%. The two groups were comparable in achieving T12 analgesic levels, block intensity, and time of onset of maximum sensory block. T12 analgesic levels were maintained for 60 minutes with prilocaine and 120 minutes with bupivacaine, whereas regression of the motor block took 135 and 210 minutes, respectively. In addition, the time to spontaneous voiding was 306 minutes with prilocaine compared to 405 minutes with bupivacaine. Both study drugs achieved equivalent sensory and motor block quality, providing adequate surgical anesthesia for at least 1 hour. However, 2% hyperbaric prilocaine was superior to 0.5% hyperbaric bupivacaine regarding faster offset, faster time to first spontaneous voiding, faster recovery room, and home release. The use of hyperbaric solutions restricts the block to only the location to be operated. Unilateral spinal anesthesia can also minimize the extent of sympathetic block, resulting in minimal disruption of cardiovascular homeostasis and reducing the incidence of clinically relevant hypotension by 5% to 7% (10).

Using low-dose morphine in combination with an anesthetic regimen for spinal anesthesia can provide optimal analgesic effects and reduce side effects. Research conducted by Koning et al. showed that the use of morphine with bupivacaine can reduce the need for IV opioids and reduce pain scores (11). Another study also suggested that the use of low-dose morphine, of about 0.1 mg morphine, can reduce pain scores after surgery compared to other analgesic regimens (12).

No literature mentions the minimum dose of prilocaine in spinal anesthesia. These studies only state that to avoid the toxic effects of prilocaine, the maximum dose that can be used is 600 mg. In this case, a dose of 2% prilocaine with a dose of 80 mg was used. In patients with

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comorbid congestive heart failure, prilocaine 2% at 80 mg plus 0.1 mg morphine produced a stable hemodynamic response and low pain scores during and after surgery.

CONCLUSION

Stable hemodynamics and thorough patient assessment are crucial in reducing morbidity and mortality during and after surgery, especially for patients with comorbidities such as congestive heart failure. The use of spinal anesthesia with a prilocaine regimen resulted in stable hemodynamics and reduced morbidity and mortality in this patient, compared to other local anesthetic regimens. Further research is needed to determine the effectiveness of prilocaine compared to other local anesthetic regimens. Nevertheless, using a safe anesthetic method and regimen tailored to the patient's comorbidities is essential for reducing mortality during and after surgery.

Acknowledgment
None

Conflict of Interest
There is no conflict of interest.

Funding Disclosure
None

Authors' Contribution
All authors have contributed to all processes in this research.

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Case Report

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) MANAGEMENT IN SEVERE COVID-19

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ABSTRACT

Introduction: The Coronavirus disease 2019 (COVID-19) caused a global pandemic and many management challenges. Acute Respiratory Distress Syndrome (ARDS) is one of the most common pneumonia complications in COVID-19 cases. ARDS in COVID-19 have worse outcomes and increased risk of intensive care unit (ICU) admission. **Objective**: This case report aims to recognize and understand ARDS management in a severe COVID-19 case. **Case Report:** A 68-year-old man with diabetes mellitus and hypertension arrived at the Emergency Room (ER) after experiencing five days of fever, cough, diarrhea with frequency of four times a day, weakness, and a positive antigen result for COVID-19 at admission. Anosmia was absent. The patient had been vaccinated for COVID-19 twice. The main problem was his desaturation of 88%, blood pressure of 156/73 mmHg, heart rate of 80x/minute, and respiratory rate of 20x/minute. However, the patient was alert and admitted to the isolation ward. After 21 days of hospitalization, the patient's condition worsened. The patient developed ARDS and was referred to the COVID ICU for 25 days and 20 days to the non-COVID ICU, where he was intubated, and a tracheostomy was performed. After 45 days of admission to the ICU, the patient's condition improved. **Discussion**: COVID-19 patients with ARDS should be immediately intubated when conditions such as dyspnea, RR>30x/min, SpO2<92% (for patients with no comorbidities) or <95% (for patients with comorbidities), unconsciousness, or shock appears. Furthermore, other conditions, such as an HR> of 120x/min and a ROX index of <3.851, should be considered an indication for intubation. **Conclusion**: Timely intubation improves the outcome of COVID-19 patients with ARDS.

Keywords: ARDS; Covid-19; Desaturation; Intubation; Management

ABSTRAK

Pendahuluan: *Coronavirus disease* 2019 (COVID-19) merupakan pandemi global dan memiliki banyak tantangan dalam tatalaksananya. *Acute Respiratory Distress Syndrome* (ARDS) merupakan salah satu komplikasi yang paling sering dari COVID-19 dengan pneumonia. ARDS pada COVID-10 memiliki luaran yang kurang baik dan sering membutuhkan perawatan di *Intensive Care Unit* (ICU). **Tujuan**: Tujuan laporan kasus ini adalah untuk memahami penanganan ARDS pada pasien dengan COVID-19. **Laporan Kasus:** Seorang laki-laki usia 68 tahun datang ke Unit Gawat Darurat dengan keluhan demam, batuk, diare 4 kali per hari, lemas, dan hasil swab antigen COVID-19 positif pada hari yang sama. Pasien tidak mengalami anosmia. Pasien telah mendapatkan vaksin COVID-19 sebanyak 2x sebelumnya. Masalah utama dalam kasus ini adalah pasien mengalami desaturasi hingga 88%. Tekanan darah pasien adalah 156/73 mmHg, *heart rate* 80 kali per menit, dan *respiratory rate* 20 kali per menit. Pasien dalam keadaan kompos mentis. Setelah perawatan selama 21 hari di rumah sakit, pasien mengalami perburukan kondisi, yaitu pasien mengalami ARDS. Pasien kemudian dirawat di bangsal ICU COVID selama 25 hari, kemudian dipindahkan ke ICU Non-COVID dan dirawat selama 20 hari. Pasien dilakukan tindakan intubasi dan trakeostomi. Setelah 45 hari perawatan di ICU, kondisi pasien membaik. **Pembahasan**: Pasien COVID-19 dengan ARDS harus segera dilakukan intubasi apabila terdapat kondisi seperti *dyspnea* dengan RR>30 kali per menit, SpO2<92% pada pasien tanpa komorbid/ SpO2<95% pada pasien dengan komorbid, pasien tidak sadar, atau terdapat tanda syok. Kondisi lain seperti HR>120x/menit dan ROX index <3,851 juga dapat menjadi pertimbangan apakah perlu dilakukan intubasi. **Kesimpulan**: Tindakan intubasi yang tepat dan sesuai indikasi dapat meningkatkan luaran pasien dengan COVID-19 dengan ARDS.

Kata kunci: ARDS; Covid-19; Desaturasi; Intubasi; Manajemen

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INTRODUCTION

The coronavirus causes disease in humans and animals. COVID-19 has emerged as one of the leading causes of death worldwide (1). People suffering from COVID-19 usually experience respiratory tract infections from mild types, such as the common cold, to severe types, such as the middle east respiratory syndrome and severe acute respiratory syndrome. The new type of coronavirus was found in Wuhan, China, in December 2019, later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2) and caused the Coronavirus disease-2019 (COVID-19) (2).

The signs and symptoms of COVID-19 are a fever of 38^0C, cough, and in severe cases, dyspnea. Dyspnea is present in almost 50% of COVID cases (Jiang et al., 2020). Individuals who traveled within the past 14 days to an infected country or had borderless contact with suspected COVID-19 cases were examined in the laboratory (2). Based on the severity of the disease, COVID-19 can be classified as asymptomatic, mild, moderate, severe, and critical.

The severity of COVID-19 is classified into the following degrees, as shown in Table 1.

Table 1. Severity Degree of Covid-19 (2)

Degree	Sign
Asymptomatic	No sign and clinical symptom
Mild	Fever, fatigue, anorexia, shortness of breath, myalgia, headache, diarrhea, anosmia, ageusia, with SpO2 >95% room air. No pneumonia
Moderate	Sign of pneumonia (fever, cough, dyspnea, takipnea) without any sign of severe pneumonia. SpO2 93-95% in room air
Severe	Signs of pneumonia such as fever, cough, dyspnea, tachypnoea, and one of the symptoms respiratory rate >30 or distress of respiratory. SpO2 < 93% in room air
Critical	Patient with Acute Respiratory Distress Syndrome (ARDS), septic and septic shock

CASE REPORT

A 68-year-old man with a weight of 65 kg arrived at the Emergency Room (ER) with a history of the fifth day of fever, cough, diarrhea four times a day, weakness, and dyspnea. The patient was still alert, and his blood saturation was 88%. His blood pressure was 156/73 mmHg, HR 80x/min, and RR 20x/min. The patient was vaccinated twice with the Sinovac vaccine for the COVID-19 virus. The patient also had a medical history of hypertension and diabetes mellitus. He was given supplemental oxygen with a binasal cannula of 4 lpm, and his blood saturation improved to 98%. The patient was admitted to the isolation ward.

Table 2. The Patient's Blood Saturation, Oxygen Supplementation, BP, HR, Temperature, and GCS During Admission

Parameter	COVID ICU	Non-COVID ICU	Post-PDT
SpO2	91-94	97-100	98-100
VM mode	PSIMV	PSIMV	PSIMV
PEEP	8	8	8
RR	22	32	26
VTE	420	306-501	500-700
FiO2	80-90	70-80	70-80
BP	150/60	90/40	130/70
HR	80-100	110-120	80

Table 3. Sputum Culture Result

Day	Bacteria	Sensitive	Resistant
21	Acitenobacter Baumanii	Amikacin	Tigecycline
46	Pseudomonas Aeruginosa	Gentamicin, cefepime, ciprofloxacin, meropenem, ceftazidime	Abstract title and contents
62	Pseudomonas Aeruginosa	Gentamicin, amikacin, cefepime, ciprofloxacin, moxifloxacin, ceftazidime	Azithromycin, meropenem

Table 4. Blood Culture Result

Day	Bacteria	Sensitive	Resistant
49	Streptomonas maltophilia	Ciprofloxacin, levofloxacin, cotrimoxazole, fosfomycin	Tetracycline, chloramphenicol

Table 5. Patient's Laboratory Parameters

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Parameter	ER	COVID ICU	Non-COVID ICU	Post-PDT
Hb	14.9	10.1	8.6	8.5
Hmt	38.9	31.1	27.1	26.6
WBC	9700	6750	8740	13540
Plt	136.000	290.000	275.555	270.000
Na	119	145	145	144
K	4.02	4.71	3.11	3.23
Cl	87	107	107	104
Alb	3.53	2.28	2.15	2.67
SGOT	104	15	34	32
SGPT	38	12	26	18
BUN	-	-	23.9	62.4
Creat	-	-	1.14	2.69
BG	157	-	127	120
PT	16.9	14.9	15.6	16.5
APTT	50.3	36.5	35.8	33.2
INR	1.17	1.01	1.06	1.13

Table 6. Blood Gas Analysis

Parameter	ER	COVID ICU	Non-COVID ICU	Post-PDT
pH	7.56	7.42	7.44	7.31
pO2	90.2	67.8	106	134
pCO2	23.2	45.4	55.1	53.7
HCO3	20.8	29.9	38	27.2
BE	0.9	5.2	14	1
SO2	98	93.5	98	99
AaDO2	118.5	566.4	-	-
FiO2	35	100	80	70
Temperature	37	36	39	36.9
TCO2	-	-	40	29

After 21 days in the ward, the patient's condition worsened. Thus, he was admitted to the COVID ICU. The patient was diagnosed with Severe COVID-19 with acute respiratory distress syndrome and intubated after three days of diagnosis. He was intubated with ETT number 7.5, a ventilator setting of PSIMV mode, inspiratory pressure of 15, P control of 20-22, and FiO2 80%. The patient also underwent insertion of central venous catheterization in the subclavian vein and the arterial line. The patient was sedated with fentanyl at a 50 mcg/hour dose.

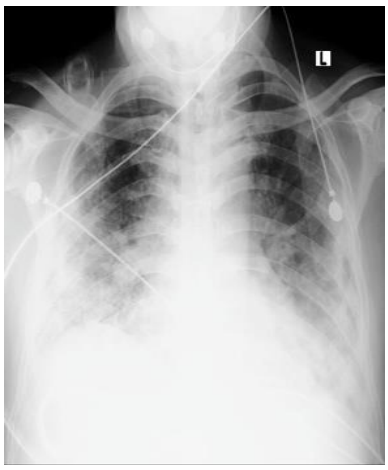

Figure 1. Patient's Chest X-ray in the Isolation Ward (before admission to the COVID ICU)

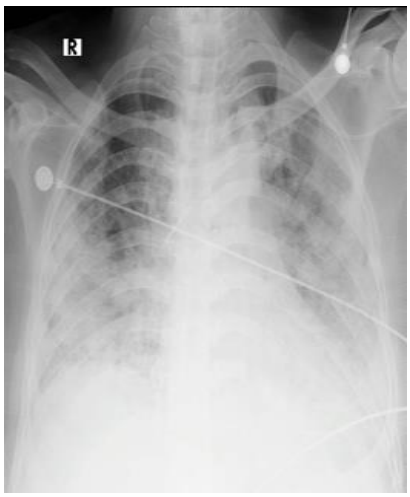

Figure 2. Patient's Chest X-ray in the COVID ICU

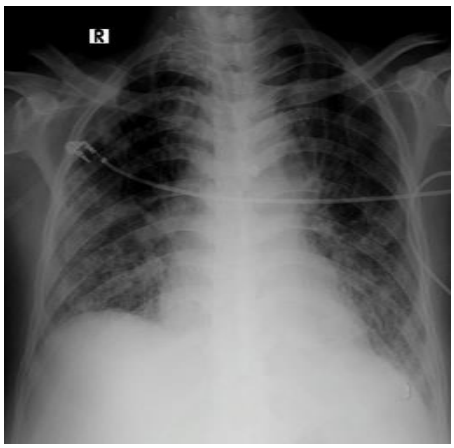

Figure 3. Patient's Chest X-ray After a Tracheostomy in the Non-COVID ICU

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The patient was initially administered favipiravir tablets in the isolation ward. It was then changed to remdesivir with a loading dose of 200 mg, followed by a 100 mg/day dose until ten days in the COVID ICU. Acetylcysteine injection was administered until 14 days, followed by 200 mg/8 hour orally. Other medication given to the patient was Vitamin C 500 mg/ 8 hours, Vitamin D 1000 IU/day, Zinc 20 mg/day, salbutamol 4 mg/12 hours, paracetamol 1000 mg when he had a fever, nifedipine 30 mg/day, omeprazole 40 mg/day, and enoxaparin 100 mg/12 hours subcutaneously until eight days, then orally. Azithromycin and fluconazole 200 mg/day were given on the patient's first day in the hospital.

The chest X-ray showed improvements in the patient's condition after 28 days of intubation. Tracheostomy was performed after 28 days of admission to the ICU. Nineteen days after the tracheostomy, the patient was transferred to the general ward with an improved condition, compos mentis.

This patient's complications in the ICU include acute kidney injury, pneumonia, hypoalbuminemia, decubitus ulcer, and rigidity of four extremities. The case report is compared with other cases in the discussion.

DISCUSSION

The patient was intubated on the 21st day (PF ratio 72.5), more than 24 hours after being diagnosed with ARDS. The Indonesian Society of Internists released their third recommendation for COVID-19 management. They stated that patients with ARDS should be immediately intubated when conditions such as dyspnea, RR>30x/min, SpO2<92% (no comorbid patient), or <95% (comorbid patient), unconsciousness, or shock appear. Another condition, such as an HR>120x/min and a ROX index of <3.851, should be considered an indication for intubation.

The fifth recommendation by the Indonesian Ministry of Health for COVID-19 management was the immediate intubation of ARDS patients (2,3,4). In this case, the patient's intubation was delayed (>24 hours after being diagnosed with ARDS) because of the family's initial refusal of intubation.

Tracheostomy was performed by the percutaneous dilatational technique (PDT) in ICU on day 49 (PF ratio after PDT was 263.2). Meanwhile, the patient's length of stay in the ICU was 45 days.

This patient had no supplemental therapy, such as tocilizumab, as the hospital did not have it in stock. Tocilizumab in the third clinical trial phase of EMPACTA (September 2020) is recommended and resulted in 44% lower complications but has no difference in 28-day mortality (tocilizumab 10.4% vs. placebo 8.6%, p: 0.5146). Other COVACTA clinical trials showed no difference in the clinical status of the patients administered tocilizumab and placebo (4,5). Immunoglobulin and plasma convalescence was not given due to the patient's critical status (6). The antibiotic was given according to the culture results.

The National Institute of Health of the United States of America released treatment guidelines for COVID-19. The panel recommends that adults with COVID-19 that were administered conventional oxygen therapy and still had acute hypoxemic respiratory failure should start therapy with a high-flow nasal cannula (HFNC) oxygen. If patients fail to respond, non-invasive ventilation (NIV) or intubation and mechanical ventilation should be initiated.

If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting

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due to the enhanced risk of exposing healthcare practitioners to SARS-CoV-2 during intubation. Pisano et al. state that signs or symptoms of significant respiratory distress or tissue hypoxia (e.g., respiratory rate above 25-30 per minute, use of accessory respiratory muscles, sweating, dyspnea, tachycardia, increased blood lactate levels, and more) are an indication for intubation in COVID patient.

Severe respiratory distress, hypoxia, and loss of consciousness are indications for intubation (7). Furthermore, advanced age, obesity, the male sex, and underlying systemic diseases such as hypertension and diabetes also increase the risk for intubation in COVID-19 patients (8) (9). Moreover, early intubation with ≤ 6 L/min of oxygen usage was associated with decreased in-hospital mortality among COVID-19 patients who required intubation (10).

CONCLUSION

COVID-19 patients should be monitored closely for acute hypoxemic respiratory failure. Supplementary oxygen should be given as needed. To improve patient outcomes, COVID-19 patients with ARDS should be immediately intubated when indications for intubation arise.

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Conflict of Interest

There is no Conflict of Interest.

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Authors' Contribution

Both of the authors contributed in the writing of this case report.

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Literature Review

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH MITOCHONDRIAL DISORDERS

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ABSTRACT

Introduction: Mitochondrial Disorders (1/4,000 patients) are rare and caused by dysfunctional mitochondria. Anesthetic consideration in patients with Mitochondrial Disorders involves careful preoperative and perioperative observations. **Objective:** To provide a brief insight into how general anesthetics interfere with mitochondrial energy formation pathways and help form precautions for anesthesiologists when managing patients with Mitochondrial Disorder. **Review:** Mitochondrial Disorder patients would experience various health problems, such as damaged cardiac functions, neurology systems, and musculoskeletal functions due to energy production disruptions by dysfunctional mitochondrial processes. Moreover, patients with Mitochondrial Disorders exhibit hyperreactivity to volatile anesthetics. **Summary:** No anesthetic strategies are found to be safe in patients with Mitochondrial Disorder yet. Therefore, anesthesiologists should remain alert when monitoring fluid choices and managing patient temperature with Mitochondrial Disorders.

Keywords: Anesthesia; Anesthetic Consideration; Anesthesiologist; General Anesthesia; Mitochondrial Disorder

ABSTRAK

Pendahuluan: Gangguan mitokondria merupakan salah satu kelainan genetik langka (1/4.000 pasien) yang disebabkan oleh disfungsi mitokondria. Pertimbangan anestesi pada pasien dengan Gangguan Mitokondria meliputi pengawasan ketat pra operasi dan perioperatif. **Tujuan**: Untuk memberikan wawasan singkat tentang bagaimana anestesi umum dapat mengganggu jalur pembentukan energi mitokondria, sehingga dapat diwaspadadi oleh para dokter spesialis anestesiologi saat menangani pasien dengan Gangguan Mitokondria. **Review:** Pasien dengan Gangguan Mitokondria akan mengalami berbagai gangguan kesehatan seperti kerusakan fungsi jantung, sistem saraf, dan fungsi muskuloskeletal akibat terganggunya pembentukan energi oleh proses mitokondria. Pasien dengan Gangguan Mitokondria menunjukkan reaksi hiperaktif (sensitif) terhadap anestesi volatil. **Ringkasan:** Belum ada strategi anestesi yang aman pada pasien dengan Gangguan Mitokondria. Dokter spesialis anestesi harus waspada daalam menentukan pilihan terapi cairan, dan pengelolaan suhu pada pasien dengan Gangguan Mitokondria.

Kata kunci: Anestesi; Pertimbangan Anestesi; Dokter Spesialis Anestesi; Anestesi Umum; Gangguan Mitokondria

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INTRODUCTION

Mitochondrial Disorders are genetic disorders caused by mutations in mitochondrial DNA (mtDNA). This disease can be passed on from parents to their offspring through maternal inheritance. It is also clinically heterogeneous, where symptoms primarily impact the central nervous system (CNS), heart, eyes, musculoskeletal, and gastrointestinal systems (1-3). Mitochondrial

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Disorder is typically considered a childhood disorder. However, the improvement in genetic laboratory testing has revealed that adult patients can also have mitochondrial disorders. Mitochondrial Disorder patients can endure anesthesia but are at risk for perioperative complications, post-operative ventilation, hemodynamic compromise, and even death (1). No anesthetic strategies have been found to be safe in patients with Mitochondrial Disorders yet (1,2). Therefore, anesthetic consideration for patients with Mitochondrial Disorders is important, and anesthesiologists should be alert when monitoring fluid choices and managing patient temperature.

REVIEW

Mitochondrial Disorder Pathophysiology and Clinical Manifestations

Mitochondrial Disorders can be caused by inheritance from the mother's gene (maternal), through an autosomal recessive or dominant gene, or de novo (4,5). This is because the mitochondrial and nuclear genomes contribute to the mitochondrial proteome (5). Different types of DNA encode the essential structural components of ETC and ATP production via oxidative phosphorylation. Oxidative phosphorylation happens in the inner mitochondrial skin. The three pathways directly involved in the protons pump for intermembrane are complexes I, III, and IV. Complex V also plays a role in the electrochemical gradient to produce ATP from ADP and Pi. Moreover, Mitochondrial Disorders can arise through a multitude of gene mutations. More mutations in mtDNA would explain stronger phenotypic penetrance and manifest in Mitochondrial Disorder.

The strict maternal inheritance of mtDNA results in homoplasmic individuals, who typically have a single mtDNA, the maternal one. However, heteroplasmy (the simultaneous presence of two or more mtDNA types in the same individual) has often been reported. Mitochondrial DNA spread has higher unpredictability since the mitochondrial genome may be analogous in all copies (homoplasmy) or diverge between copies (heteroplasmy) (1,6). Nevertheless, heteroplasmy has unexpected effects on offspring, and the heteroplasmy rate cannot always correlate with clinical phenotype. Heteroplasmy can primarily occur through somatic mutagenesis during an individual's lifetime and through leakage of paternal mtDNA in the zygote during fertilization (7). Recent studies using modern sequencing techniques have revealed that heteroplasmy from somatic mutations might be prevalent among some individuals. Heteroplasmy and the normal variation in baseline metabolic demand mechanisms explain variable clinical manifestations between individuals. Therefore, we cannot use a generalized anesthetic plan for Mitochondrial Disorder for all patients. Additionally, there is a point at which the cell can tolerate mitochondrial damage. Hence, metabolic dysfunction and symptoms occur after mutations exceed the threshold. For example, the mitochondrial disorder Leigh syndrome is a progressive neurodegenerative disorder that can be caused by 80 different genetic mutations (1,3,8).

A patient is suspected of respiratory chain disorder when they have these risks and exhibit the following symptoms: (1) consanguineous parents; (2) maternal inheritance; (3) more than one affected system; (4) progressive disease; (5) worsening state due to energy imbalance (catabolic states, for example, nausea, diarrhea, dehydration, fever, extended fasting, surgical procedure); or become affected by drugs metabolized at the

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mitochondria. The vast symptoms of Mitochondrial Disorder in childhood include epilepsy, encephalopathy, stroke, brain hyperintensities in T2 and FLAIR, sensory neural hearing loss, cardiac hypertrophy, muscle weakness, ophthalmic problems, and tubulopathy (6).

Furthermore, patients with Mitochondrial Disorders do not manifest only one disease; they frequently overlap with multiple syndromes. Mortality typically increases with respiratory failure complications. Patients also generally have acute symptoms or remain stable until triggered by fever, infection, pregnancy, or anesthesia (1). Childhood-onset Mitochondrial Disorder has significantly higher mortality than adult-onset Mitochondrial Disorder. Adult-onset Mitochondrial Disorder is insidious; its symptoms include progressive vision impairment, ataxia, cardiomyopathy, and cardiac impairment. Recently, next-generation sequencing (NGS) has allowed for the diagnosis of genetic mutations by revealing new genetic impairments in more than 300 genes (1,5,8,9).

A muscle biopsy is the gold standard for diagnosing Mitochondrial Disorders (1). Mitochondrial dysfunction is characterized by ragged-red fibers. Analysis can also be conducted for specific mtDNA mutations. However, DNA sequencing is also essential for diagnosis. Patients with Mitochondrial Disorders have genetic mutations in their mtDNA or nuclear DNA or > 70% depletion of mtDNA (for primary mitochondrial depletion syndrome).

Anesthetic Considerations in Mitochondrial Disorder Patients

The anesthetic management of Mitochondrial Disorder patients involves strict preoperative and perioperative observations. Mitochondrial Disorder patients treated with propofol are not at risk for severe hyperthermia. However, they must not be treated by prolonged propofol infusion as it affects mitochondrial function via multiple pathways. Therefore, propofol use must be restricted. Succinylcholine is also an absolute contraindication because of hyperkalemia and myotonic risks. Non-depolarizing agents must be used with caution, given their random effects. Vein route injection and volatile anesthetics should be gradually infused while observing the patient's clinical symptoms or administered via electroencephalogram (EEG) (1).

Moreover, Mitochondrial Disorder patients have a higher risk of postoperative respiratory depression because of allergies to anesthetics and opioids, pre-existing musculoskeletal conditions, and unpredictable reactions after neuromuscular blocking agents' application. Patients with pre-existing conditions with bad cough reflexes or recurring pneumonia may benefit from using preoperative non-invasive positive pressure ventilation (NIPPV) instead. The protein target hypothesis describes a general anesthetic mechanism through ion channels or receptors. Overall, the different effects between highly varied chemical agents and the adverse events of anesthetics are still debated (1,11).

Preanesthetic Assessment

Mitochondrial Disorder patients typically need surgical treatment for accessory path ablation, a pacemaker, or implanted cardioverter defibrillation (ICD) insertion (1). Mitochondrial Disorder is a chronic condition, so patients must correct their ophthalmology impairment, ear tympany membrane implantation, profound brain stimulation,

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gastro-jejunal tubes, fractures surgery, thyroidectomy, or organ transplantation. Before surgical treatment, patients also must pass a holistic assessment, and an interdisciplinary consultation with other specialists is required to build an anesthetic plan.

Next, patients and families are informed about postoperative ventilation risks, mainly for chest or upper abdomen intervention. Neurologic assessments must be documented so the clinician can compare preoperative neurologic deficits and intraoperative events. Neuromuscular changes must also be assessed because of hypotonus, spastic, myoclonic, and rigid muscles. Moreover, clinicians must be aware of the undiagnosed Mitochondrial Disorder in adult patients with pre-existing muscle weakness, especially in increased lactate and multisystem impairments (10). Neuropathy should be examined and documented. The history and management of seizures should be noted to prepare for the patient's ketogenic diet. Additionally, the patient is recommended to continue their antiepileptic drugs until surgery (1).

Furthermore, total anesthesia is strongly favored, as vein sedation brings unnecessary risk. The impaired lung is not the cause of the respiratory disturbance, but neuromuscular and central control of breathing affects by the impaired lung, resulting in respiratory impairment and atelectasis (1). Patients can also have bulbar muscle impairment, difficulty swallowing, stridor and snoring, cough, and hoarseness. Polysomnography can diagnose obstructive sleep apnea (OSA), central apnea, and hypoxia & hypocapnia (2). Children with the disease have also shown sleep-related breathing disturbances. The patient's baseline pulse oximetry and arterial blood gas should also be checked to assess the baseline carbon dioxide (CO_2) if SpO_2 is under 95% (12).

Hypertrophic cardiomyopathy occurs in 40% of primary Mitochondrial Disorders, and conduction abnormalities are present in >10% of Mitochondrial Disorders. Wolff Parkinson White (WPW), premature ventricular contractions, and preexcitation supraventricular arrhythmias are also present in Mitochondrial Disorders. A complete AV block might happen. Thus, access to external pacing and defibrillation is needed, and a low threshold is required for preoperative pacemaker insertion. Atropine, epinephrine, and isoproterenol should also be available. Before the surgery, patients should do check-ups, especially electrocardiograms and echocardiograms. Invasive arterial blood pressure monitoring is also recommended in Mitochondrial Disorder patients with cardiomyopathy for quick access to blood sampling (1).

Furthermore, Mitochondrial Disorder patients usually have chronic malnutrition, electrolyte imbalances, or growth development impairments, such as growth faltering. Endocrine instabilities are also common, along with diabetes mellitus, adrenal insufficiency, and low thyroid and parathyroid hormone levels (1). Mitochondrial Disorder patients have an impaired ability to use alternative energy pathways in the hypoglycemia state. Therefore, preoperative fasting is limited to 2 hours to reduce glucose depletion, hypovolemia, and overreliance on fat energy pathways. The surgery must be performed as soon as possible to inhibit energy storage usage (1,2).

In some cases, extended fasting can reduce pulmonary aspiration risk; but in Mitochondrial Disorder patients, metabolic and surgical inflammatory stress increases metabolic

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impairment and lactate acidosis risks (1). Hence, dextrose infusion added to the perioperative lactate-free infusion is recommended for Mitochondrial Disorder patients. Dextrose is used, except if the patient is on a ketogenic diet or would experience a destructive impact if consuming higher glucose. Normoglycemia must prevent excessive glycolytic oxidation and a rise in the lactate plasma. Additionally, perioperative hemodynamic sustainability and optimum oxygenation are essential to maintain energy formation (13).

Intraoperative Anesthetic Assessment

The intraoperative anesthetic assessment always focuses on reducing metabolic disturbance, sustaining hemodynamics, and enhancing the postoperative respiratory state. Dextrose-based maintenance fluids are recommended, especially for children with Mitochondrial Disorder, to deliver proper energy supplementation (13). In patients with Mitochondrial Disorders, regular glucose level checks should be done. Moreover, as they have weakened lactate metabolisms, lactate in fluids should be evaded. Serum lactate and pH should be checked regularly. Normal saline + 5% dextrose is the choice for maintenance fluid (1).

Temperature instabilities are poorly endured in Mitochondrial Disorder patients. Temperature observations and usage of air and fluid warmers are recommended in the perioperative phase. Shivering depletes energy reserves and causes severe myotonic or paradoxical paralysis. Perioperative complications, such as malignant hyperthermia (MH), affect 1/30,000 children and cause spasms of the musculoskeletal after exposure to volatile anesthetics, such as halothane, resulting in muscle myopathy, acidosis, arrhythmia, hyperkalemia, hyperthermia, and death (2,14).

Mitochondrial Disorder patients show diaphragm and extra respiratory muscular tissue impairment, which can cause significant respiratory problems. This mechanism can happen rapidly, slowly, or on a progressive pathway. Rapid sequence intubation (RSI) using the muscle relaxant succinylcholine is not recommended because of hyperkalemia and myotonic crisis risks. Thus, anesthetic agents needed to be titrated to minimize hemodynamic disturbance. Inhalation inductions must be conducted slowly and gradually (1).

Processed electroencephalogram (EEG) generates numerical brain electrical activity and prevents inaccurate doses of anesthetics. Processed EEGs and the Bispectral Index (BIS) can help determine specific patient anesthetic depth because of the risk of hypersensitivity to these agents (1,15). Short-acting agents are recommended, and careful observation should be used for patients with respiratory problems and their limited capacity to endure acidosis. Sevoflurane should be better than desflurane and isoflurane because desflurane and isoflurane cause a more significant ventilatory depression. Anesthetic plans that rely on spontaneous ventilation are contraindications, as spontaneous ventilation can cause energy store depletion and airway obstruction. To prevent complications, evaluations to reduce nausea and vomiting, lubrication, and eye protection are recommended. Tourniquets and pressure points are also contraindications due to reduced tissue oxygen delivery (1).

Postoperative Consideration

Postoperative assessment has the same procedure as preoperative assessment. It focuses on sustaining energy and optimizing respiratory functions. Patients with impaired

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renal and liver function changes the pharmacologic clearance and postpone recovery from anesthesia. Therefore, careful observation should be done until the patient's status is returned. Pulmonary irrigation, physiotherapy, and prompt mobilization can prevent postoperative atelectasis and help restore muscle strength. Postoperative analgesia is recommended to prevent excess oxygen usage, but clinicians must also ensure that the patient's respiratory and cough mechanisms are safe. Opioid-sparing anesthetics are helpful, and short-acting opioids are recommended (1,12).

Pharmacologic Suggestions

Inhalational Agents

Volatile anesthetics can reduce mitochondrial complex I's ability in vitro (1). On the other hand, general anesthetics (volatile and parenteral) reduce mitochondrial function. Mitochondrial Disorders, especially complex I defect, show hypersensitivity to volatile anesthetics, such as sevoflurane. Research has shown that mitochondrial complex I deficiencies reduce the effective anesthetics dose to half. Meanwhile, imperfections in fatty acid processes do not affect the sensitivity of volatile anesthetics (12).

Volatile agents (halothane, enflurane, isoflurane, desflurane, and sevoflurane) cause anesthetic preconditioning (APC) (2). Previous studies have shown that desflurane has the most significant protective effect of all the volatile agents, followed by sevoflurane and isoflurane. It is also reported that other drugs, such as morphine and lidocaine, have preconditioning properties. Moreover, APC arises if reactive oxygen species (ROS) progress after volatile anesthetics, preventing hypoxia and apoptosis, myocardium ischemic damage, and partial ETC inhibition, resulting in low numbers of oxidative stress in complex I (sevoflurane), or complex III (isoflurane) (16).

Mitochondrial Disorder patients have an allergy to volatile anesthetics. Regional anesthesia could lessen opioids and other usages. Local anesthetics are suitable for Mitochondrial Disorder patients as there is no clear association between MH and the disease. Reduced end-tidal (ET) sevoflurane dosages are also needed to achieve a loss of consciousness on induction in childhood-onset Mitochondrial Disorders, unlike the typical value of 3.0 until 3.5% sevoflurane needed in healthy children (17).

Volatile anesthetics have rapid elimination, which is beneficial in Mitochondrial Disorders. Volatile anesthetics use exhalation for elimination, allowing an expedient reoccurrence of mitochondrial function after the agent is withdrawn. Thus, low blood/gas solubility drugs, such as desflurane, are beneficial. However, many practitioners avoid volatile agents in Mitochondrial Disorders because of myopathies associated with MH. Nevertheless, the Malignant Hyperthermia Association of the United States (MHAUS) recommends using volatile anesthetics in Mitochondrial Disorder (1,2).

Intravenous Agents.

Propofol damages mitochondrial inhalation by uncoupling oxidative phosphorylation from the ETC, distributing long-chain fatty acids across the cell membrane via acyl transferase I (CPT I), and limiting the production of acetyl-CoA for ATP production via mitochondrial respiration. PRIS occurs at mean doses of more than 4 mg/kg/hour for 48 hours. The symptoms are metabolic impairment, arrhythmias, rhabdomyolysis, hepatomegaly, and dyslipidemia. The PRIS pathophysiology might be caused by

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mitochondrial defects in ATP production. Abnormal response to Propofol in children must be screened for the possibility of Mitochondrial Disorder. In Mitochondrial Disorder patients, postponed recovery is seen in patients administered with short-term Propofol. However, in a retrospective review, most of the cohort received Propofol anesthetic without rhabdomyolysis (2,18).

The Mitochondrial Medicine Society (MMS) consensus mentions that Propofol is contraindicated or restricted to short-term use (< 1 hour). Multiple authors elaborate on their research that Propofol induction doses and limited propofol boluses are well tolerated, except in Mitochondrial Disorder patients with a ketogenic diet (18). Patients using TIVA with dexmedetomidine and remifentanil as non-triggering anesthetic had decreased adverse events associated with mitochondrial stress and metabolic impairment (18,19,20).

The modified-Delphi technique supports the usage of ketamine, barbiturates, midazolam, or other benzodiazepines. Barbiturates, ketamine, and midazolam obstruct complex I activity. Benzodiazepines impact mitochondrial permeability, increasing apoptosis, and barbiturates uncouple oxidative phosphorylation (13,20). Case reports support dexmedetomidine use for continuous infusion or intermittent bolus. However, the recovery was delayed because of prolonged clearance. Thus, the judicious use of these medications is not harmful in a patient with Mitochondrial Disorder (19).

Moreover, opioids are generally well tolerated in these populations. Short-acting opioids or opioid-sparing are suggested. Opioids reduce the propofol dose to achieve a loss of consciousness, unrestrained movement, and hemodynamic responses to noxious stimuli. However, patients may have extra sensitivity to opioids because of the upregulation of endorphins. Therefore, remifentanil has been recommended, and the modified Delphi recommends fentanyl as a safe choice for Mitochondrial Disorder patients (21).

Paralytic and Reversal Agents.

Succinylcholine is contraindicated in Mitochondrial Disorder patients due to their common myopathy and myotonic crisis. Hyperkalemia and death can occur because of the upregulation of skeletal muscle nicotinic acetylcholine receptors in Mitochondrial Disorder patients. Thus, close neuromuscular observation (e.g., train-of-four) should be done (1,22).

Neostigmine has shown adverse effects in Mitochondrial Disorder patients and is not an ideal reversal agent. Besides muscarinic side effects, neostigmine triggers a myotonic crisis. On the other hand, sugammadex is a gamma-cyclodextrin that is used in neuromuscular inhibitor reversals. This sugammadex reversal has a beneficial effect: a complete return of paralysis in pre-existing conditions patients. However, further research is recommended to establish safety and dosing recommendations in general Mitochondrial Disorder patients. Total avoidance of neuromuscular blockade is recommended (22).

Local Anesthetics.

Local anesthetics are good for infiltration and periphery nerve blockade. However, bupivacaine use is contraindicated in Mitochondrial Disorder. Bupivacaine affects mitochondrial bioenergetics by disrupting acyl transferase, causing fatty acid beta-oxidation inhibition and the reduction of oxidative phosphorylation. These mechanisms have been proposed as the source of bupivacaine-related

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cardiotoxicity across all populations (1). Ropivacaine and lidocaine are favored over bupivacaine due to their minimal inhibition of these biochemical pathways (1,2). Nevertheless, clinicians should administer the minimum dose of ropivacaine and lidocaine to avoid cardiotoxicity in all patients, especially in Mitochondrial Disorder patients (1).

For Mitochondrial Disorders patients with Kearns-Sayre syndrome, neuraxial anesthesia is safe. The anesthetics have been administered without signs of respiratory impairment, hemodynamic instability, or arrhythmia. The main advantages of neuraxial anesthesia are reduced oxygen consumption and acidosis. However, the increased energy demand causes the need to closely monitor the patient's temperature, hydration, and glucose levels (1).

SUMMARY

Mitochondrial Disorders are rare and are complex multisystem diseases. Anesthetic considerations for Mitochondrial Disorder have resulted in several problems with clinicians. Hence, careful preoperative and perioperative planning is recommended. MMS recommendations are available for safe perioperative Mitochondrial Disorder patients' management. The recommendations include the judicious use of volatile anesthetics while observing the depth of anesthetic drugs. Meanwhile, perioperative optimization is done by reducing fasting, carefully selecting the fluid of choice, and temperature management. Nevertheless, further research is needed to provide more recommendations on anesthetic considerations for Mitochondrial Disorder patients.

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Conflict of interest

The authors declare no conflict of interest.

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Authors' Contribution

All authors have contributed to all processes in this study.

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Systematic Review and Meta-Analysis

A SYSTEMATIC REVIEW AND META-ANALYSIS OF PARACERVICAL BLOCKS AS A PERIOPERATIVE STRATEGY IN REDUCING POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LAPAROSCOPIC HYSTERECTOMY

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ABSTRACT

Introduction: Perioperative strategies to reduce postoperative pain are important for enhancing patient satisfaction. However, further research and trials has sparked ongoing debates of various strategies regarding efficacy and safety. **Objective:** This study aims to improve evidence-based strategies regarding the effect of paracervical anaesthetic blocks in patients undergoing laparoscopic hysterectomy. **Materials and Method:** A systematic literature search was conducted through PubMed, Google Scholar, and ScienceDirect for RCTs in laparoscopic hysterectomy patients administered paracervical blocks and those given placebos. The quantitative analysis of pooled relative risk and mean difference with a 95% confidence interval were performed using the Review Manager 5.4 software in the random-effects model or fixed-effects model forest plot. **Results:** Based on four RCTs included in the analysis, there were significant differences in overall postoperative pain scores assessed by VAS (Visual Analogue Scale) [MD = -0.82, 95%CI (-1.47 to -1.06), p = 0.01]. The subgroup analysis also showed significant differences in VAS pain scores at 30 min and 1 hour post-operation [MD = -2.13, 95% CI (-3.09 to -1.16), p = 0.0001] and [MD = -2.55, 95% CI (-4.29 to -0.81), p = 0.004]. However, there were insignificant results in adequate pain control [RR = 7.90, 95%CI (0.39 to 158.67), p = 0.18], length of hospital stay [MD = 0.01, 95%CI (-0.52 to 0.54), p = 0.96], additional analgesics requirement at 24 hours [RR = 0.88, 95%CI (0.55 to 1.39), p=0.58], and perioperative complications [RR = 0.90, 95%CI (0.56 to 1.47), p = 0.68].**Conclusion:** This meta-analysis provides evidence that the administration of paracervical block in patients undergoing laparoscopic hysterectomy is associated with a reduction of postoperative VAS pain score but not associated with the length of hospital stay, adequate pain control, additional analgesics requirement at 24 hours, and perioperative complications.

Keywords: VAS; Paracervical Block; Laparoscopic; Hysterectomy; Meta-Analysis.

ABSTRAK

Pendahuluan: Strategi perioperatif untuk mengurangi nyeri pasca operasi penting untuk meningkatkan kepuasan pasien. Namun, perdebatan yang sedang berlangsung tentang berbagai strategi mengenai efikasi dan keamanan muncul karena uji coba lebih lanjut telah dipublikasikan. **Tujuan:** Penelitian ini bertujuan untuk meningkatkan strategi bukti mengenai efek anestesi blok paraservikal pada pasien yang menjalani histerektomi laparoskopi. **Bahan dan Metode:** Pencarian literatur sistematis dilakukan pada PubMed, Google Scholar, dan ScienceDirect untuk studi RCT pada pasien histerektomi laparoskopi yang diberikan blok paraservikal dibandingkan dengan plasebo. Analisis kuantitatif risiko relatif gabungan dan perbedaan rata-rata dengan interval kepercayaan 95% dilakukan dengan menggunakan perangkat lunak *Review Manager 5.4* dalam model *random-effects* atau *fixed-effects forest plot*. **Hasil:** Berdasarkan empat studi RCT yang dimasukkan dalam analisis, terdapat perbedaan yang signifikan pada skor nyeri pasca operasi secara keseluruhan yang dinilai dengan VAS (*Visual Analogue Scale*) [MD = -0,82, 95%CI (-1,47 to -1,06), p=0,01]. Analisis subkelompok juga menunjukkan perbedaan signifikan pada skor nyeri VAS pada 30 menit dan 1 jam pasca operasi [MD = -2.13, 95%CI (-3.09 to -1.16), p=0.0001] dan [MD = -2.55, 95%CI (- 4,29 to -0,81), p=0,004]. Namun, terdapat hasil yang tidak signifikan pada kontrol nyeri yang adekuat [RR = 7.90, 95%CI (0.39 hingga 158.67), p=0.18], lama perawatan di rumah sakit [MD = 0.01, 95%CI

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(-0.52 hingga 0.54), p= 0,96], kebutuhan analgesik tambahan pada 24 jam [RR = 0,88, 95%CI (0,55 hingga 1,39), p=0,58], dan komplikasi perioperatif [RR = 0,90, 95%CI (0,56 hingga 1,47), p=0,68]. **Kesimpulan:** Meta-analisis ini memberikan bukti bahwa pemberian blok paraservikal pada pasien yang menjalani histerektomi laparoskopi berhubungan dengan penurunan skor nyeri VAS pasca operasi tetapi tidak berhubungan dengan lama tinggal di rumah sakit, kontrol nyeri yang adekuat, kebutuhan analgesik tambahan pada 24 jam, dan komplikasi perioperatif.

Kata kunci: VAS; Blok Paraservikal; Laparoskopi; Histerektomi; Meta-Analisis.

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INTRODUCTION

Perioperative strategies under the control of anaesthesiologists, surgeons, or related physicians to reduce postoperative pain are important for enhancing patient satisfaction (1). Laparoscopic hysterectomy is a minimally invasive procedure for obstetrics and gynaecology surgery. It has more reported advantages than traditional abdominal hysterectomy, but its postoperative discomfort still requires attention (2,3). Postoperative pain after laparoscopic hysterectomy associated with incisional and visceral pain is most intense 30 min after surgery (2). Several strategies to reduce postoperative pain were researched, such as opioid use, transverse abdominis plane (TAP) blocks, intraperitoneal local anaesthetic, and port site infiltration (4). Visceral pain is a very intense, dull, or heavy inner pain caused by tissue manipulation during surgery. Although visceral pain dominates over incisional pain, it has often been neglected during postoperative pain management (2,4).

Sensitization of this painful stimulus is transmitted by the pelvic visceral nerve plexus, derived from the hypogastric plexus, due to the stimulation of the Lee-Frankenhauser plexus located within the uterosacral ligament. Local drug infiltration by paracervical block is a potentially promising strategy because it can block the pelvic afferent sensory nerve fibres (5,6). Moreover, infiltration drugs using bupivacaine were reported beneficial because its onset action was 15 minutes, and its lasting effect was up to 9 hours (7).

However, current literature reported inconsistent results regarding the efficacy of paracervical block, and the available randomized trials (RCTs) could not answer whether the paracervical block is required for pain reduction after laparoscopic hysterectomy. Therefore, this study aims to improve the evidence-based strategies approach by conducting a systematic review and meta-analysis to provide the best answer regarding the clinical effects of administering paracervical blocks as a perioperative strategy in reducing postoperative pain in patients undergoing laparoscopic hysterectomy.

MATERIAL AND METHOD

Database Search and Study Selection

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (8). A systematic literature search was performed through PubMed, Google Scholar, and ScienceDirect using the following keywords: paracervical block, hysterectomy, and laparoscopic hysterectomy. We only included articles that match our eligibility criteria based on PICOS: (i) Population: patients who underwent laparoscopic hysterectomy; (ii) Intervention: Paracervical block using bupivacaine; (iii) Comparator: Placebo; (iv) Outcomes: postoperative pain scores measured by the

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visual analogue scale (VAS), length of hospital stay, adequate pain control, additional analgesics requirement at 24 hours, and perioperative complications; (v) Study design: Randomised controlled trials (RCTs).

The literature search was conducted in August 2022 without any year restrictions. All results from the electronic databases were stored in Rayyan.ai to undergo the selection process (9). Two independent reviewers performed the selection process based on title and abstract screening then the full-text selection was performed based on the eligibility criteria. Any conflicts during article selection were discussed with all authors.

Data Extraction

All included studies underwent data extraction by two independent reviewers. The main outcome used in this study is postoperative pain scores measured by VAS. There were many secondary outcomes, such as length of hospital stay, adequate pain control, additional analgesics requirement at 24 hours, and perioperative complications. Other data extracted from the selected studies include the year of publication, country, surgical procedure approach, population, operating time, body mass index (BMI), intervention, and administration procedure of paracervical block. Any controversies between data extraction were discussed with other authors.

Risk of Bias Assessment

We assessed the risk of bias for each study using the Cochrane Risk of Bias 2 (ROB 2) tool (10). This tool consists of several domains, such as randomization sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each domain was graded as “low risk”, “unclear risk”, and “high risk” of bias. The risk of bias assessment was conducted by two reviewers independently. Any difference in grading was discussed with other authors.

Data Synthesis and Analysis

The selected studies were analysed qualitatively and quantitatively using meta-analysis. We performed a meta-analysis using the Review Manager (RevMan) 5.4 software (Cochrane Collaboration, Oxford, UK) with 95% confidence intervals (CI). Pooled mean difference (MD) was performed to calculate postoperative pain scores and the secondary outcome of length of hospital stay. In addition, the pooled risk ratio was used to calculate other secondary outcomes, such as adequate pain control, additional analgesics requirement at 24 hours, and perioperative complications. The random effects model and fixed effects model forest plot were used based on heterogeneity. The random effects model was used when heterogeneity was high ($I^2 \geq 50\%$), and the fixed effects model was used when heterogeneity was low ($I^2 < 50\%$)(11).

RESULTS AND DISCUSSION

Study Selection

Based on our database search, we found 1891 articles from Google Scholar, ScienceDirect, and PubMed. We conducted the duplicate screening automatically using Rayyan.ai and then underwent title and abstract screening. A total of 7 articles were checked for full-text screening eligibility after the title and abstract screening. Quantitative analysis using meta-analysis was performed for four selected articles. Figure 1 shows the PRISMA Flow Diagram.

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Study Characteristics and Risk of Bias

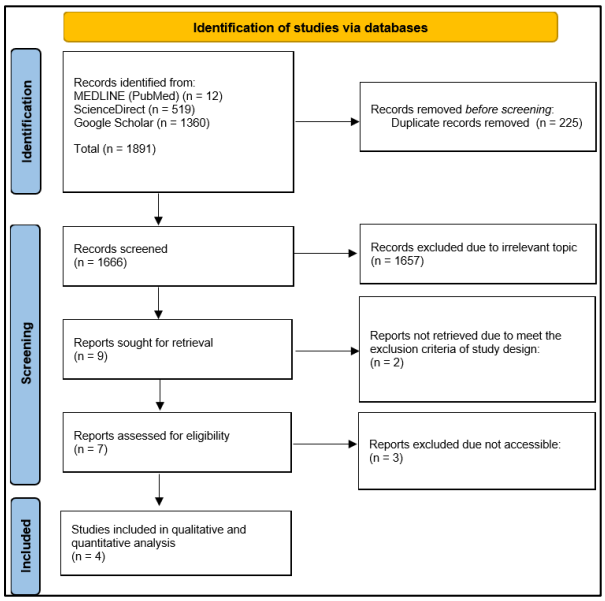

Figure 1. PRISMA Flow Diagram

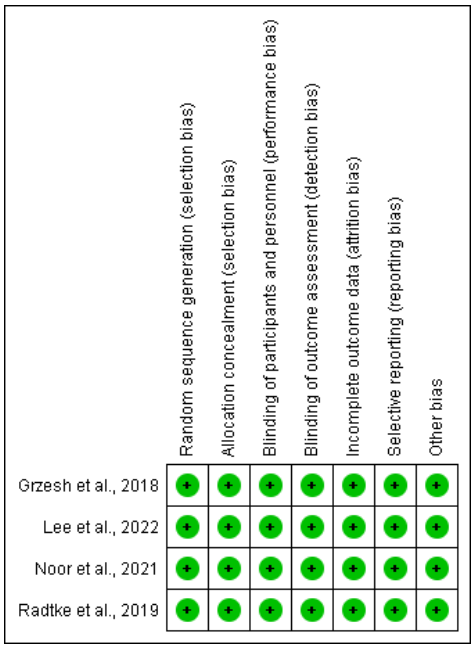

Figure 2. Risk of Bias of Included Studies

Table 1 summarises all the included RCT studies. The sample size varied between 41 to 132 samples. Two studies were conducted in the USA (12,13), one in India (14), and one in South Korea (15). The risk of bias assessment was conducted using the Cochrane ROB 2 tool, and its result is presented in Figure 2. All included studies were found to have a low risk of bias. Figure 2 shows the risk of bias assessment by the ROB 2 tool.

Outcomes: Postoperative Pain Scores

Three studies reported that the overall postoperative pain scores assessed by VAS were significantly different between groups [pooled MD = -0.82, 95% CI (-1.47 to -1.06), p = 0.01]. Heterogeneity between studies was also high (I^2 = 80%). Moreover, the accordance results showed by subgroup analysis that paracervical block administration was statistically significant for reducing postoperative pain scores at 30-minutes [pooled MD = -2.13, 95%CI (-3.09 to -1.16), p < 0.0001] with low heterogeneity (I^2 = 0%). The subgroup analysis of VAS pain scores 1 hour after surgery showed a significant difference between groups [pooledMD = -2.55, 95% CI (-4.29 to -0.81), p = 0.004] and a high heterogeneity was observed (I^2 = 66%). Figure 3 shows a forest plot for postoperative pain between the experimental and placebo groups.

Outcomes: Length of Hospital Stay

Two studies observed length of hospital stay, and the results demonstrated no significant difference between the groups [pooled MD = 0.01, 95%CI (-0.52 to 0.54), p = 0.96] and low heterogeneity between the studies was observed (I^2 = 0%). Figure 4 shows the forest plot for the length of hospital stay between the experimental and placebo groups.

Outcomes: Adequate Pain Control

Two studies reported adequate pain control for patients with VAS scores ≤4 or ≤5, where 32/51 patients in the experimental group and 5/50 in the placebo groups showed improvement in pain control. However, this analysis revealed that administering a paracervical block is not statistically

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significant for improving the number of patients with adequate pain control [pooled RR = 7.90, 95%CI (0.39 to 158.67), p = 0.18]. The analysis also had considerable heterogeneity (I^2 = 78%). Figure 5 shows the forest plot for postoperative pain between the experimental and placebo groups.

Table 1. Characteristics of included studies

Study (Country)	Surgical approach	Population	Operating time		BMI		Intervention	Administration of paracervical block
			Experimental	Control	Experimental	Control		
Grzesh et al., 2018 (USA)	Laparoscopic supracervical hysterectomy	132	89 (69–116) min	99 (73.5–117) min	27.2 ± 5.7	29.1 ± 6.9	20 ml 0.25% bupivacaine with 1:200,000 epinephrine	After intubation but before the first skin incision at 2, 5, 7, and 10 o'clock depth of 2 cm
Radtke et al., 2019 (USA)	Total laparoscopic Hysterectomy with GA	41	119.7 (15.5) min	132.5 (33.1) min	30.0 ± 9.8	32.7 ± 9.8	10 ml 0.5% bupivacaine with epinephrine	Injected into the cervical stroma at 3 and 9 o'clock with a depth of 2 to 3 cm
Noor et al., 2021 (India)	Total laparoscopic hysterectomy	60	4,038.0 ± 961.8 s	3,730.0 ± 483.6 s	26.9 ± 4.1	25.2 ± 1.9	10 mL of 0.5% bupivacaine	5 mL each at the 3 and 9 o'clock positions, with a depth of 2 cm
Lee et al., 2022 (South Korea)	Total laparoscopic hysterectomy with or without salpingo-oophorectomy	86	85.7 ± 20.6 min	83.5 ± 18.6 min	24.2 ± 4.2	24.4 ± 5.8	10 mL of 0.5% bupivacaine with 1:200,000 epinephrine vs 10 ml of normal saline	Injected into the cervical stroma at 3 and 9 o'clock with a depth of 1 to 2 cm after insertion but before fixation of the uterine manipulator

Outcomes: Additional analgesics requirement at 24 hours

Three studies reported additional analgesics requirements 24 hours after a laparoscopic hysterectomy, with 86/199 events in the experimental groups and 93/193 in the placebo groups. Overall, the paracervical block was not associated with a reduction in additional analgesics requirement at 24 hours in terms of opioid or narcotics and other pain medication [pooled RR = 0.88, 95%CI (0.55 to 1.39), p = 0.58] with high heterogeneity (I^2 = 75%). The subgroup analysis conducted for opioids or narcotics and other pain medication showed no significant difference [pooled RR = 0.73, 95% CI (0.41 to 1.31), p=0.29 and RR = 1.57, 95% CI (0.80 to 3.09), p=0.19]. The heterogeneity was high for the opioids or narcotics subgroup (I^2 = 90%) and low for other pain medication (I^2 = 0%). Figure 6 shows the forest plot for postoperative pain between the experimental and placebo group.

Outcomes: Perioperative complications

Two studies reported postoperative complications with 22/111 events in the experimental groups and 23/107 events in the placebo groups. These results showed that the

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pooled estimates were not statistically significant [pooled RR = 0.90, 95% CI (0.56 to 1.47), p = 0.68]. There was mild heterogeneity (I^2 = 0%). Figure 7 shows the forest plot for postoperative pain between the experimental and placebo groups.

Discussion

A meta-analysis of 4 RCTs involving 319 patients was conducted to provide evidence of the clinical effect of paracervical block in patients who underwent a laparoscopic hysterectomy. This study showed evidence of the benefit of administering paracervical block using bupivacaine compared to placebo to reduce postoperative pain scores, as assessed by VAS, for 30 minutes, 1 hour, and overall pain scores. Additionally, local anaesthetic preoperatively infiltrating the paracervical tissue is a potential pain control method because of tissue issues during a laparoscopic hysterectomy (13)

Paracervical block infiltration contributes to inhibiting the hypogastric plexus that is transmitted by the Lee-Frankenhauser stimulation in the uterosacral ligament. This inhibition is beneficial for reducing postoperative painful sensations (5). Although the results reported that paracervical block significantly reduces postoperative pain scores, it contradicts the outcome for the number of patients with adequate pain control. Radtke et al. reported successful pain control using criteria of an average pain score of 4 or less (13). Meanwhile, Noor et al. reported that adequate pain control was achieved when the mean VAS score was ≤5 (14).

Next, in this study, the length of hospital stay did not statistically differ between groups. Radtke et al. reported that it is important to understand that the majority of case decisions for hospitalization are not based on pain after surgery (13). Several patients who required additional analgesics at 24 hours were administered opioids and narcotics, and other pain medication. The analysis demonstrated no evidence for the benefit of paracervical blocks with overall additional analgesics requirements at 24 hours. These results align with the subgroup analysis for opioids, narcotics, and other pain medication. Grzesh et al. reported that even though the additional analgesics requirement was not significant at 24 hours, previous studies have demonstrated that the paracervical blocks resulted in a significant reduction in narcotics requirement for 7-days and 8-days post-operation and a significant reduction in other pain medication requirements for 6-days post-operation (12).

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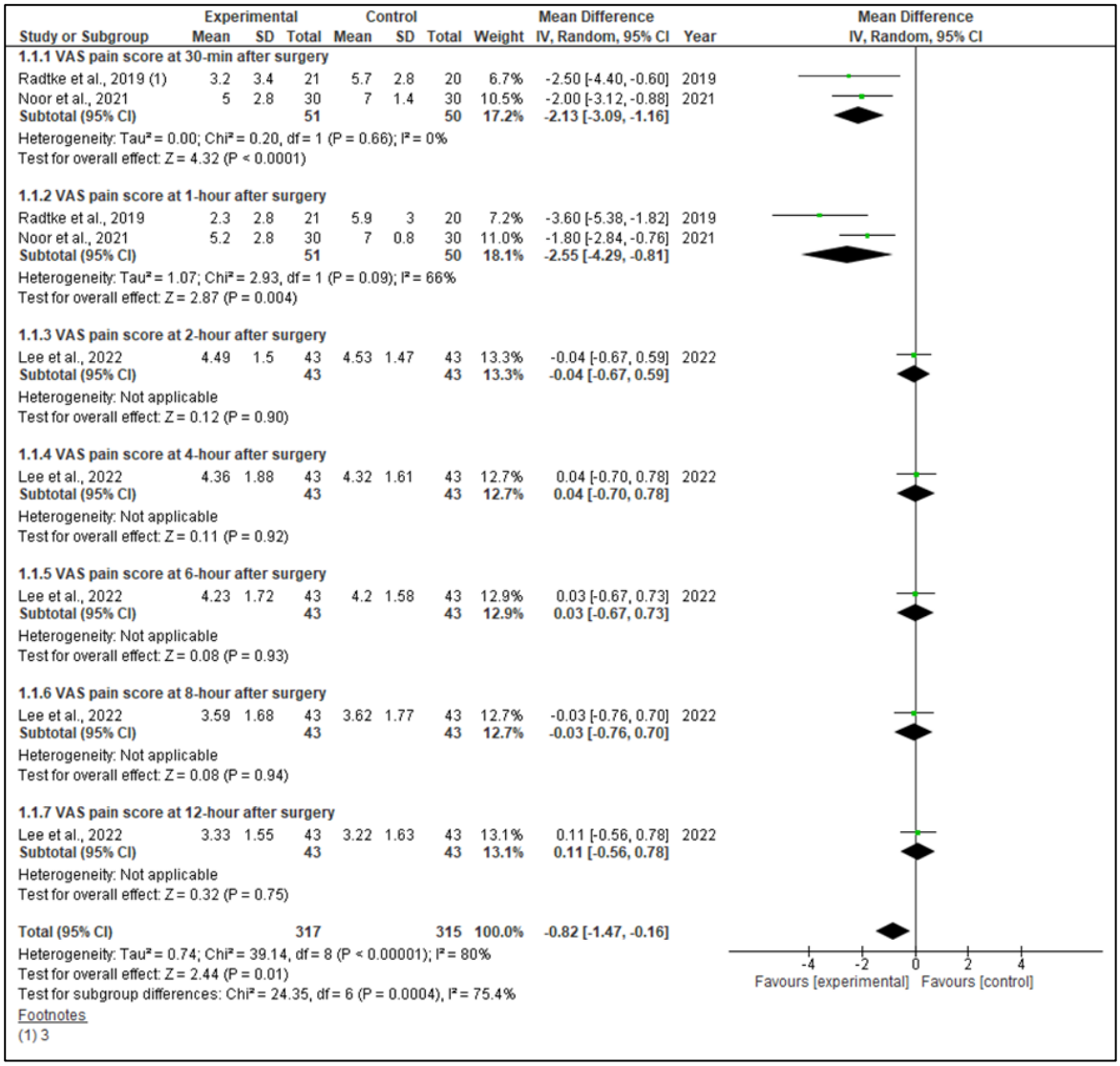

Figure 3. Forest Plot for Postoperative Pain Between the Experimental and Placebo Groups

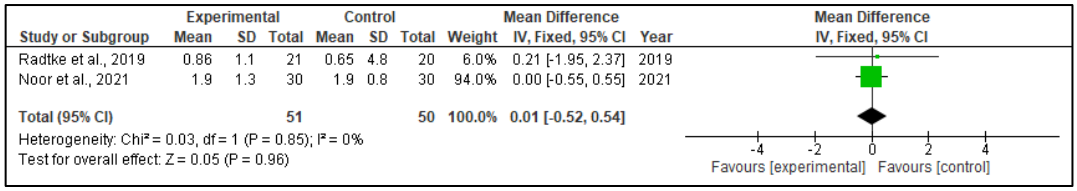

Figure 4. Forest Plot for The Length of Hospital Stay Between the Experimental and Placebo Groups

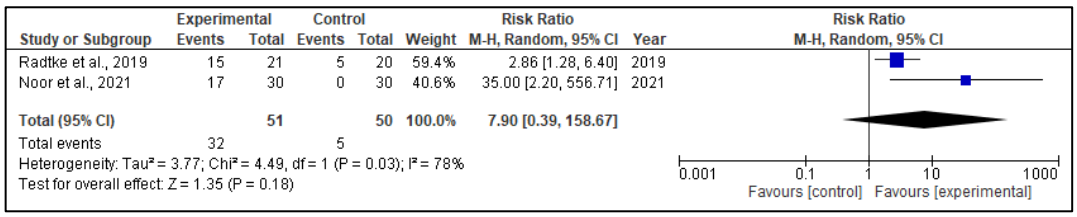

Figure 5. Forest Plot for Adequate Pain Control Between the Experimental and Placebo Groups

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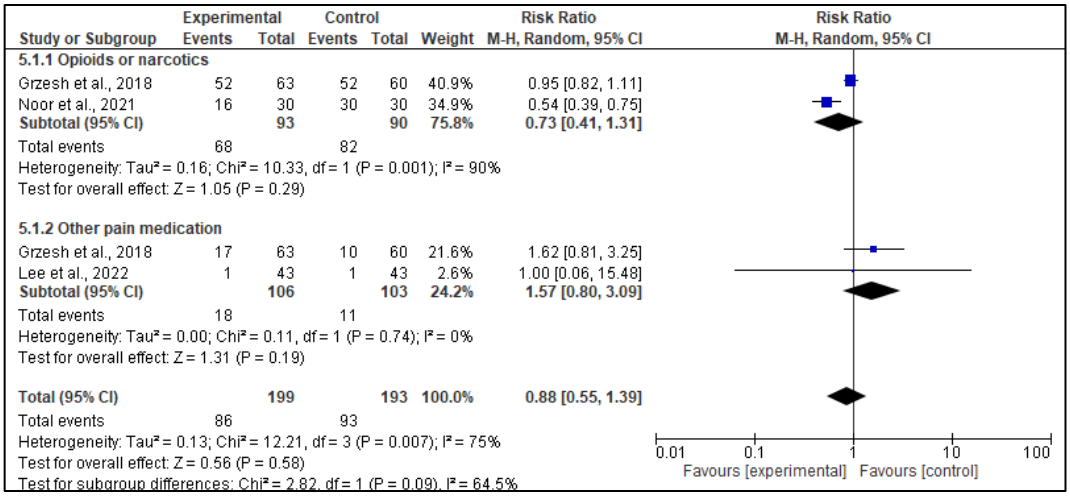

Figure 6. Forest Plot for Additional Analgesics Requirement at 24 Hours Between the Experimental and Placebo Groups

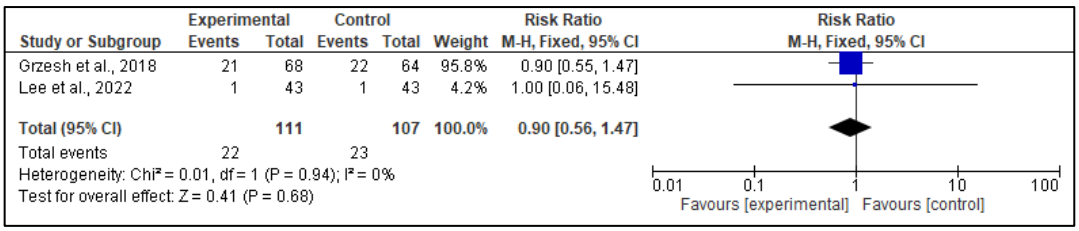

Figure 7. Forest Plot for Perioperative Complications Between the Experimental and Placebo Groups

Noor et al. reported that the administration of paracervical blocks contributed to decreasing the need for additional opioid analgesic in the first 1 hour after surgery by 47% (14). Patients given paracervical blocks reported a higher ratio of perioperative complications despite the results showing no significant difference. Grzesh et al.'s study reported that patients experienced perioperative complications up to 6 weeks after surgery based on the Clavien-Dindo classification. Most of the recorded complications were Dindo grade 1 or 2, and there were no conversions to laparotomy (12). Additionally, Lee et al. reported that postoperative compilations developed in each group, including an ileus in the experimental group and a vaginal cuff infection in the placebo group (15).

This systematic review and meta-analysis were conducted with the most up-to-date literature search and used clinically important outcomes from RCT studies. The study selection process and appraisal of included studies were performed by two reviewers independently and showed a low risk of biased judgment.

Nevertheless, this study has some limitations. First, the quantitative analysis was conducted with a small sample size and limited studies. Second, there were different approaches in terms of the laparoscopic hysterectomy procedure. Third, postoperative pain assessed using pain scores is considered a subjective method for evaluation. Furthermore, multicentre RCTs with a large population and various outcomes are required to gain deeper insight.

CONCLUSION

This meta-analysis provides evidence that the administration of paracervical blocks in patients undergoing laparoscopic hysterectomies is effective in reducing

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postoperative pain measured by VAS but is not associated with perioperative complications, length of hospital stay, adequate pain control, and additional analgesics requirement at 24 hours.

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Conflict of Interest

The authors declared that there is no conflict of interest in this study.

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Authors' Contributor

All authors have contributed to several processes in this study.

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- Amini S, Najafi MN, Karrari SP, Mashhadi ME, Mirzaei S, Tashnizi MA, et al. Risk factors and outcome of acute kidney injury after isolated cabg surgery: A prospective cohort study. Brazilian J Cardiovasc Surg. 2019; 34(1): 70–5.

2. A book

McKnight CL, Burns B. Pneumothorax. In: StatPearls. StatPearls Publishing; 2021.

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