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ORIGINAL RESEARCH INTENSIVE CARE

Ketamine combined with dexmedetomidine reduces neutrophil lymphocyte ratio (NLR) in critically ill COVID-19 patients; a pre-experimental study

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ABSTRACT

Background & objective: About 20% of patients with COVID-19 admitted to the intensive care unit (ICU) need ventilatory support under sedation using dexmedetomidine and ketamine. Ketamine has an anti-inflammatory effect and is expected to suppress immune cells. A high neutrophil-lymphocyte ratio (NLR) is associated with a severe stage of the disease. We compared NLR between COVID-19 patients under sedation with dexmedetomidine alone or with dexmedetomidine combined with ketamine.

Methodology: This pre-experimental study involved a control group of patients receiving dexmedetomidine (n = 10) and the intervention group receiving dexmedetomidine and ketamine (n = 10) for sedation. NLR was evaluated before and after 24 h of sedation with the study drugs.

Result: The patients' NLR increased significantly at 24 h after sedation using sole dexmedetomidine from 9.01 to 15.62 (P > 0.05). The combination of dexmedetomidine and ketamine significantly reduced NLR from 11.22 to 8.61 (P = 0.026). Both groups experienced a decrease in neutrophil count (P > 0.05). The lymphocyte count increased significantly in the intervention group (P = 0.025) and decreased in the control group.

Conclusion: There is a significant NLR difference between a patient receiving dexmedetomidine sedation compared dexmedetomidine combined with ketamine. A combination of dexmedetomidine and ketamine reduces NLR compared to sole dexmedetomidine in critically ill COVID-19 patients.

Keywords: COVID-19, dexmedetomidine, ICU, ketamine, neutrophil lymphocyte ratio, NLR

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1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA novel beta coronavirus, first identified in December 2019 in Wuhan, China, as the cause of coronavirus disease 2019 (COVID-19). Severe clinical manifestations of COVID-19 include fever, cough, and shortness of breath. The China Disease Control and Prevention Team reported

that of 44,500 confirmed patients, 80% developed mild pneumonia, 14% developed severe pneumonia, and 5-10% progressed to critical illness and death. About 20-30% of patients hospitalized for COVID-19-related pneumonia require intensive care and treatment with a ventilator. In severe pneumonia, complications often appear as Acute Respiratory Distress Syndrome (ARDS) and fall into a state of respiratory failure (5-10%), which requires intensive care and assistive devices.[1]

The success in managing COVID-19 depends on the speed of screening and treatment provided. Clinical and laboratory parameters, including leukocytes, monocytes, neutrophils, lymphocytes, platelets, interleukins, neutrophil-lymphocyte ratio (NLR), and other inflammatory cytokines, help the physician to decide the appropriate treatment.[1,2] Previous studies stated that higher levels of leukocytes, neutrophils, and NLR were directly proportional to the severity of COVID-19.[1,2] Critically ill COVID-19 patients exhibit higher NLR than non-ICU patients. Xia et al. found that about 80% of the infected SARS-CoV-2 patients with bilateral pulmonary involvement had elevated NLR.[3]

The complete blood count is an inexpensive, routine, and practical laboratory test useful in disease diagnosis and prognosis. NLR can indicate systemic inflammation because neutrophils and lymphocytes are significant in immunology and inflammation. Inflammation plays an important role in the proliferation and angiogenesis; it is crucial in the development and progression of the disease; even when the white blood cell count is in the normal range, NLR has been shown to play a role as a predictor of the prognosis of chronic and acute inflammatory processes.[4]

Several studies have shown that patients with more severe clinical manifestations have higher NLR. This indicates that NLR can be an initial screening test for COVID-19 patients. The threshold NLR for disease progression, i.e., NLR > 3.3, was independently associated with more severe COVID-19 (HR: 2.46, 95% CI 1.98-4.56). Furthermore, NLR > 3.3 was associated with lower survival compared with NLR < 3.3 (NLR > 3.3: 6.3 days and NLR < 3.3: 13.5 days).[3]

Critically ill patients admitted to the ICU require analgesia and sedation to provide adequate oxygenation and ventilation. Several drugs are often used for sedation, such as benzodiazepine (midazolam), fentanyl, propofol, and dexmedetomidine. Dexmedetomidine can be used as a sole agent or combined with midazolam or opioids, reducing the need for sedatives and other analgesics. Several studies have documented that dexmedetomidine can reduce the pro-inflammatory response to stress-induced anesthesia and patients in septic states.[5]

Ketamine is an ideal anesthetic and sedative agent for maintaining hemodynamics.[6,7] It can also suppress pro-inflammatory cytokines and apoptosis and increase intracellular calcium.[8,9] In the hyper-inflammatory phase, ketamine can reduce NLR. In contrast, it can reduce the risk of secondary infection in the hypo-inflammatory phase. However, no further research has been done on this.[10] Ketamine also inhibits the oxidative function of macrophages, which means that ketamine inhibits the signalling function of macrophages and the bactericidal ability of macrophages. In addition, ketamine also inhibits neutrophils, which are involved in cytokine production, free radical scavenging, and pathogens phagocytosis. An *in vivo* study of ketamine found that all neutrophil roles are inhibited. Ketamine also inhibits the diapedesis of neutrophils to the side of the injury, thereby reducing the adhesion ability of neutrophils. Currently, ketamine is expected to be developed as an immunotherapy agent for COVID-19.[11] Therefore, we conducted a pre-experimental, comparative study of the NLR in the patients receiving sole dexmedetomidine sedation alone with patients receiving dexmedetomidine combined with ketamine in COVID-19 patients admitted to the COVID-19 ICU.

2. METHODOLOGY

This study was a true pre-experimental study with a pretest-posttest type of control group design, and conducted in November-December 2021. The research was approved by the Health Research Ethics Committee of Dr Saiful Anwar General Hospital, Malang, Indonesia (No. 400/024/K.3/302/2021). Inclusion criteria was COVID-19 positive patients (through RT-PCR tests) with severe or life-threatening clinical conditions, age 18-65 y, patient and patient's family willing to sign an informed consent to participate in the study. Exclusion criteria was the patient and/or the patient's family refusal to sign the informed consent to participate in the study, pregnant patients, a history of hypersensitivity to ketamine, a history of end-stage liver failure, and patients identified as 'Do not resuscitate' (DNR) status.

The sample was allocated using simple a double-blind random sampling. Twenty subjects were divided into the control group (n = 10) and the treatment group (n = 10). The control group received the sedating drug dexmedetomidine 0.3 µg/kg/h. The treatment group received sedation with dexmedetomidine 0.3 µg/kg/h infusion and the addition of 0.2 mg/kg bolus therapy followed by a ketamine 0.2 mg/kg/h infusion. The variables observed were the laboratory results of neutrophil-lymphocyte ratio (NLR) at zero hours before treatment and 24 h after treatment administration (post-test). The NLR was calculated by dividing the absolute

Table 1: Results of the basic characteristics of the research sample

Variable	Mean (CI 95% for mean) / n (%)		Normality	P-value
	Control group	Treatment group		
Age	51 (45-57 y)	52 (46-58 y)	√	0.788
• < 20	0	0		
• 20-29	0	0		
• 30-39	0	0		
• 40-49	4	4		
• 50-59	6	7		
• > 60	0	0		
BMI (n)	32 (30-34)	33 (31-35)	√	0.476
• < 18.5	0	0		
• 18.5-24.9	0	0		
• 25-29.9	0	0		
• > 30	10	11		
Gender			-	0.466
• M	7 (70)	6 (60)		
• F	3 (30)	4 (40)		
Comorbid			-	0.593
• No comorbidity	5 (50)	4 (40)		
• Hypertension	1 (10)	1 (10)		
• Hypotension + DM	3 (30)	0		
• Hypertension + DM	0	5 (50)		
• Hypertension + DM + Heart disease	1 (10)	0 (0.0)		

count of neutrophils by the absolute count of lymphocytes following the blood sample test.

The study results were statistically analyzed using the two-free sample T-test, Mann-Whitney test, paired two-sample T-test, and Wilcoxon test using SPSS 18 (IBM Statistic, USA) with α = 5% and a confidence interval of 95%.

3. RESULTS

The data was collected from 20 study subjects. The mean age of the treatment group was 52 y, while in the control group it was 51 y. The mean BMI was 32 kg/cm^2 in the control group and 33 kg/cm^2 in the treatment group. The majority of study subjects were male, both in the control and treatment groups. Hypertension, along with diabetes mellitus was the most common comorbidity. The table above also describes the patient's onset and initial oxygen supplementation upon arrival in the ICU. We present an onset as the means of days patients feel the initial symptoms until they are admitted to the intensive care unit. The patients in the control groups were admitted to the ICU six days after initial symptoms, while those in the treatment group were admitted to the ICU on the fifth day after the initial symptoms. Four patients in the control group received Non-invasive ventilation (NIV) for initial oxygen therapy, five were intubated, and one received high flow

Table 2: Results of the physiological and laboratory investigations of the research sample

Variable	Mean (CI 95% for mean) / n (%)		Normality	P-value
	Control group	Treatment group		
Oxygenation	NIV = 4 (40%) Intubation = 5 (50%) HFNC = 1 (10%)	NIV = 2 (20%) Intubation = 7 (70%) HFNC = 1 (10%)	-	0.518
Onset	6	5.6	√	0.767
SOFA	154.0 (109.7-198.3)	154.9 (116.1-193.7)	√	0.973
Hb	11.72 (10.91-12.53)	11.64 (10.95-12.32)	√	0.860
Leucocytes	11205 (7363-15047)	9849 (7979-11719)	X	0.888
Procalcitonin	1.61 (0.73-2.49)	1.74 (0.88-2.47)	√	0.907
Ferritin	325.9 (134.0-517.8)	298.7 (140.7-392.8)	√	0.562
PaO_2	87.80 (77.23-98.37)	81.11 (74.08-88.47)	√	0.257
Pf Ratio	168 (96-261)	204.3 (144-251)	√	0.332
SpO_2	90.9 (88.3-93.5)	92.33(90.6-93.1)	√	0.467

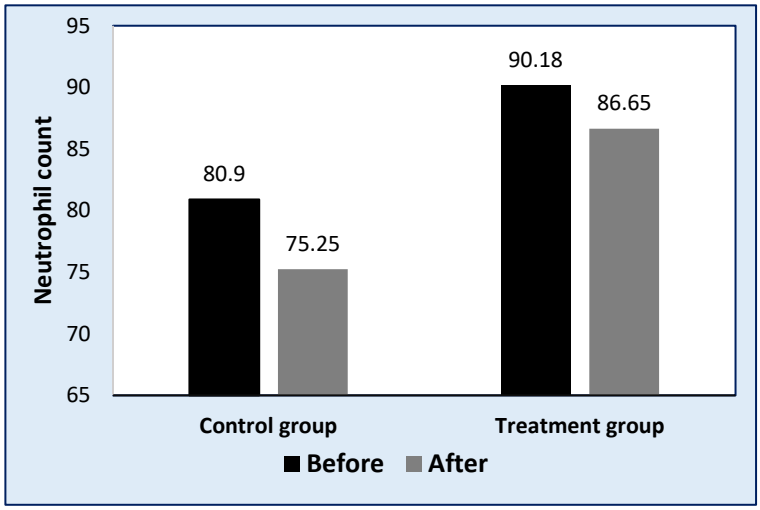

Figure 1: Comparison of neutrophil levels before and after treatment (Source: Prepared by the author)

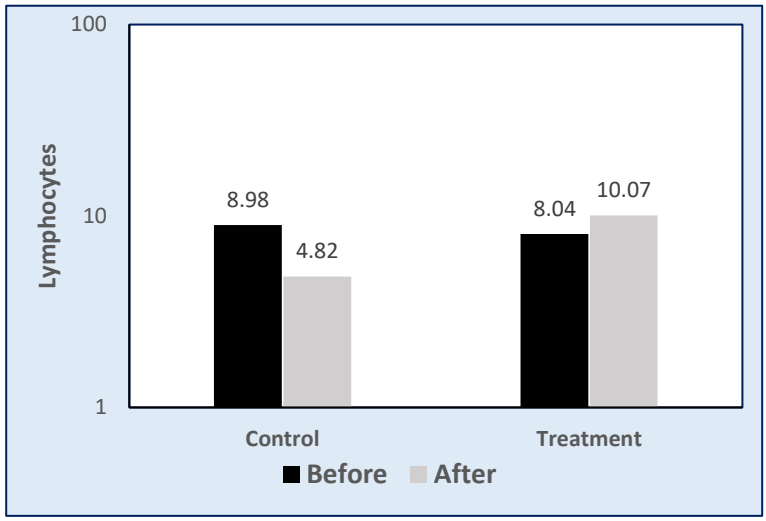

Figure 2: Comparison of the lymphocytes of the two groups before and after treatment (Source: Prepared by the author)

nasal cannula (HFNC). In the treatment group, two received NIV, eight were intubated, and one had HFNC.

Based on the two-sample t-test, several variables, including age, BMI, Onset, SOFA Score, Neutrophils, Hb, leukocytes, procalcitonin, ferritin, PaO_2, and SpO_2), are homogenous (P > 0.05).

The mean neutrophil count from both groups tended to decrease after being treated by either drug/s. Dexmedetomidine decreased neutrophil levels from 80.9 to 75.25 (P > 0.05). In the treatment group, dexmedetomidine with ketamine decreased neutrophil levels from 90.18 to 86.65 (P > 0.05). However, the differences were statistically not significant (Figure 1)(Table 2).

The mean of lymphocytes in control group decreased from 8.98 to 4.82 (P > 0.05). However, in the treatment group, the lymphocyte levels significantly increased from 8.04 to 10.07 (P = 0.025) (Figure 2) (Table 2).

n the control group, the administration of dexmedetomidine increased the NLR from 9.01 to 15.62 (P = 0.138). The administration of dexmedetomidine and ketamine in the treatment group experienced a significant reduction in NLR from 11.22 to 8.61 (P = 0.026) (Table 2). The mean NLR values of the dexmedetomidine group and the dexmedetomidine group plus ketamine showed a significant difference (P = 0.03).

. 4. DISCUSSION

This study compares NLR in critical COVID-19 patients in the ICU. In critically ill COVID-19 patients, administering a combination of dexmedetomidine and ketamine leads to a reduction in NLR compared to using dexmedetomidine alone. It suggests a potential synergistic effect between dexmedetomidine and ketamine in modulating the immune response in these patients. Such findings could pave the way for more effective treatment strategies targeting immune dysregulation in severe COVID-19 cases.

According to the study, the majority of the subjects were male. This is in accordance to the study by Padkin et al. (2003), which found that most COVID-19 patients in the

Table 3: Comparative test results in both groups

Parameters	Control Group			Treatment Group		
	Before (0 h)	After (24 h)	P-value	Before (0 h)	After (24 h)	P-value
Lymphocytes (/mL)	8.98	4.82	0.057	8.04	10.07	0.025*
Neutrophil (/mL)	80.9	75.25	0.402	90.18	86.68	0.222
NLR	9.01	15.62	0.138	11.22	8.61	0.026*

ICU are male (58.8%).[12] This is also in line with several publications that state that on an evidence base of COVID-19, men have a higher risk and mortality rate than women.[13] The difference in the number of males compared to female patients is related to high levels of pro-inflammatory cytokines and sex hormones androgens in men, which can suppress cell immune responses and decrease cardiovascular function.[14,15]

The mean age in the group receiving dexmedetomidine combined with ketamine was 52 y, and 51 y in the group only receiving dexmedetomidine. The studies conducted in Europe show an age range of 50-64 y having the risk of the severity of COVID-19 infection.[16]

Both groups have a BMI above 30 kg/m^2. This is also in accordance with research conducted by the American Heart Association in 2020, which states that obesity is a risk factor for COVID-19 infection. The degree of obesity will also aggravate the risk factors for COVID-19. A previous study in China found that abnormal BMI, including undernutrition and obesity, had a higher

mortality risk.[17] Similarly, a Norwegian study with a 15-year follow-up showed that a high BMI has a greater risk of vascular infection compared to a lower BMI.[18]

In both groups, hypertension and diabetes mellitus were the most common comorbidities. The American Journal of Emergency Medicine stated that evidence-based comorbid factors such as diabetes mellitus and hypertension were the most frequent in confirmed COVID-19 patients treated at New York Hospital.[19] This is explained by the Trevelin et al. 2017 study that there is an impairment of innate and adaptive immune responses in diabetic patients. These conditions contribute to the increased growth of micro-organisms that eventually develop into sepsis.[20] In more detail, Koh (2012) described diabetes as a result of impaired neutrophil chemotaxis, adhesion, and intracellular killing. In addition, individuals with diabetes also have humoral defects (both an antibody response and complement opsonization) and phagocytosis that play a role in resistance to pathogenic micro-organisms. Disruption of these factors is one of the causes of worsening the COVID-19 patient's prognosis.[21]

In the dexmedetomidine group, the majority of patients were admitted to intensive care and received oxygenation six days after initial symptoms. In contrast, patients receiving dexmedetomidine and ketamine were admitted five days after initial symptoms. This is in accordance with Carlos et al. in 2020, which state that the incubation period for COVID-19 varies from 2 days to 2 weeks after the viral exposure.[22] According to Li et al., it was found that symptoms of COVID-19 infection appeared after an incubation period of about five days.[22]

For initial oxygen therapy, the majority of both groups were intubated. Oxygenation is based on the clinical and laboratory parameters after the patient arrives in the ICU. The American Journal of Emergency Medicine stated that using NIV as initial oxygenation therapy for COVID-19 patients was associated with better recovery rates and success.[19]

In this study, the administration of dexmedetomidine combined with ketamine increased lymphocyte levels. This is in accordance with the theory that ketamine plays a role in increasing lymphocytes by inhibiting the release of anti-inflammatory cytokine agents and preventing the presence of neutrophilia if a viral or bacterial infection causes a secondary infection. Previous studies have also stated that ketamine has a suppressive effect on inflammation and is widely used in treating sepsis patients.[8,9]

Administration of dexmedetomidine alone and dexmedetomidine combined with ketamine tended to reduce neutrophil levels but were not statistically significant. Ketamine in vivo inhibits all these neutrophil roles. In addition, ketamine also inhibits the diapedesis of neutrophils to the site of the injury, thereby reducing the adhesion ability of neutrophils.[22]

In this pre-experimental study, the use of sedatives dexmedetomidine combined with ketamine significantly had lower NLR than patients who received dexmedetomidine only. However, sole dexmedetomidine administration increased NLR. In recent studies of COVID-19, NLR is a reliable marker for disease severity and mortality.[23] In critically ill patients, high NLR is associated with high mortality and longer intensive care stays due to high systemic inflammation and stress responses.[24]

In critically ill COVID-19 patients, high NLR becomes a problem because it can worsen the prognosis. Several sedatives affect the immune system and are related to the NLR level since they involve neutrophil and lymphocyte count.[25] This gives an idea to combine two sedatives to modulate the immune response in critically ill COVID-19 patients. Dexmedetomidine could reduce lymphocyte T CD4 and CD8, dendritic cells, and myeloid-derived suppressor cells (MDSCs).[26] It is proved by the lymphocyte count in the sole dexmedetomidine group.

Ketamine affects the immunogenicity of neutrophils, impairment of cytotoxic lymphocytes, and promotes inflammatory cell apoptosis.[27] Ketamine has a beneficial effect on the immune system; thus, in the future, it might be the first option for sedation in critically ill patients or dysregulated inflammatory and immune responses patients in the ICU.

5. LIMITATIONS

This study contains some limitations, including the minimal number of samples due to the limited number of cases and access to COVID-19 patients. However, the significant decrease of NLR in COVID-19 patients who received dexmedetomidine and ketamine gives a positive insight into critically ill COVID-19 patients and provides an excellent outcome. This pre-experimental study gives an overview of ketamine use in COVID-19 management, which can be considered to justify the use of ketamine as sedative other than dexmedetomidine and part of the management of COVID-19 patients. Since this study is pre-experimental, further study with more samples will be done to provide sufficient evidence.

6. CONCLUSION

Ketamine combined with dexmedetomidine significantly reduces NLR in critically ill COVID-19 patients. This combination offers better response in COVID-19 management in the intensive care unit.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

AZF, AAN: Conceived and designed the experiments; conducted the study; analyzed and interpreted the data

BMS, TAS: Conducted the study; analyzed and interpreted the data; manuscript preparation and editing

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