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**Original Article**

# Continuous Ketamine Administration Decreases Monocyte Count in Sepsis Patients in Intensive Care Units

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**ABSTRACT**

**Background:** Cytokines storm becomes the most common cause of mortality in sepsis patients treated in the intensive care unit (ICU). Cytokines storm is characterized by an excessive elevation in the immunocompetent cells, including monocyte. Ketamine, as a sedating agent, has immunosuppressive properties. This study was conducted to determine the effect of ketamine on monocyte count in septic patients in the ICU.
**Methods:** This is a quantitative case-control study of 30 patients treated in the ICU. The study subjects were divided into control (n=15) and treatment (n=15) groups. The treatment group received ketamine HCl therapy at 0.3 mg/kg body weight/hour. The mean monocytes were counted at 0, 24, and 48 hours post-therapy. Data analysis used an independent sample t-test with α=5%.
**Result:** Administration of ketamine therapy in septic patients treated in the ICU showed a decrease in the monocytes during observation from 0 to 48 hours post-therapy. Administration of ketamine at 48 hours had a significantly lower monocyte (5.21%) compared to control (7.67%) (p=0.012).
**Conclusion:** Ketamine administration reduces the monocytes count in septic patients treated in the intensive care unit. Ketamine is expected to be a therapeutic option in sepsis patients.

Keywords: sepsis, ketamine, monocytes, intensive care unit

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## INTRODUCTION

The high mortality rate for sepsis, especially in the intensive care unit (ICU), has become a world health problem.[1] In the United States, more than 500,000 sepsis sufferers each year continues to increase and causes more than 175,000 death each year.[2] In Europe, 750,000 people suffer from severe sepsis, with a mortality rate of around 30% to 35%. Septic shock and multi-organ failure resulting in poor outcomes.[3] The pathophysiology of septic shock is well known. However, septic shock therapy is still limited, and the mortality of patients with septic shock remains high.

The innate immune system is the first line of defense mechanism against pathogens.[4] The activation of the immunocompetent cell, including macrophages, monocytes, natural killer cells, dendritic cells, and endothelial cells mediates the innate immune response to respond to pathogens or their components.[5] Activated immune cells also secrete pro-inflammatory mediators such as cytokines interleukin (IL-1, IL-6, IL-8), tumor necrosis factor-α (TNF-α), prostaglandins, and histamine.[6] These mediators act on vascular endothelial cells and cause vasodilation, increased vascular permeability, and recruitment of neutrophils to the tissue.[7] The coagulation cascade is activated locally through the up-regulation of endothelial tissue factor and decreased thrombomodulin and its antithrombotic products.[8]

Ketamine is one of the most rational anesthetic and sedative agents for patients with sepsis because of its ability to maintain hemodynamics.[9] Giving a single dose of ketamine can significantly reduce the monocyte count in the sepsis model group of mice. Ketamine also suppresses pro-inflammatory cytokines, apoptosis, and increases intracellular calcium.[10] In the hyperinflammatory phase, ketamine can also reduce anti-inflammatory cytokines such as IL-10 in the hypoinflammatory phase. Ketamine was thought to reduce the risk of secondary infection in the hypoinflammatory phase. However, there has yet to be further research on this hypothesis.[7] Therefore, ketamine is expected to be developed as a candidate for immunotherapy in sepsis. The effect of ketamine on the number of monocytes activated by septic conditions has also not been widely studied. Therefore this study was conducted to

determine the effect of ketamine on the monocyte count of sepsis patients treated in the intensive care unit (ICU).

## METHODS

This study is a quantitative study with a case-control design to determine the effect of ketamine on the monocyte count of sepsis patients in the ICU. This research has been approved by the health research ethics committee of Dr. Saiful Anwar General Hospital (No. 400/025/K.3/302/2021).

The sample inclusion criteria included ventilated septic patients with SOFA score > 2, patients aged >18 years, and patients without definitive antibiotics. Exclusion criteria included patients with pregnancy, patients with autoimmune disorders (such as Systemic lupus erythematosus, rheumatoid arthritis, and immune thrombocytopenia), patients with chronic inflammatory disorders (such as inflammatory bowel disease and sarcoidosis), patients with malignancies (such as leukemia), patients receiving therapy (such as ziprasidone, granulocyte colony-stimulating factor (G-CSF), radiation therapy, and anti-thymocyte globulin), the patient has a history of hypersensitivity to ketamine, has a history of end-stage liver failure, patients with tachyarrhythmias, and patients identified as Do Not Resuscitate (DNR).

The sampling method uses a probability sampling technique. We enrolled 30 sepsis patients treated in the ICU. The study consisted of 2 sample groups, control and treatment groups, with a total sample of 15 patients in each group. The treatment group received Ketamine HCl syringe therapy 0.3 mg/kg body weight/hour. The control group received standard sedation therapy while in the ICU. Monocyte examination was performed at 0, 24, and 48 hours post-therapy. Monocyte counts were done through complete blood count measurement. Statistical analysis uses the independent sample t-test to determine the difference in the number of monocytes in the control and treatment groups. Statistical analysis using SPSS Statistic 20 (IBM Statistics, USA) with α=5%.

## RESULT

The results showed a difference between the monocyte count in the sepsis patients who received ketamine therapy and those who did not receive ketamine. There was a significant difference in the monocytes count at 48th-hour post-therapy (Table 1).

**Table 1**. Comparison of the monocyte count in the different observation time

| Time observation | Monocyte count | | |
|---|---|---|---|
| | Control (%) (n=15) | Treatment (%) (n=15) | p-value |
| 0 hour | 6.75 | 8.34 | p>0.05 |
| 24 hour | 7.07 | 5.80 | p>0.05 |
| 48 hour | 7.67 | 5.21 | p= 0.012 |

The trend of monocyte count in the treatment group was different from the control group. In the control group (without ketamine therapy), there was an increase in monocytes starting at 0, 24, and 48 hours of observation. In the treatment group, there is a decrease in the monocyte count starting at 0 hours of observation (Figure 1). This result shows a good outcome from giving ketamine therapy to sepsis patients treated in the ICU.

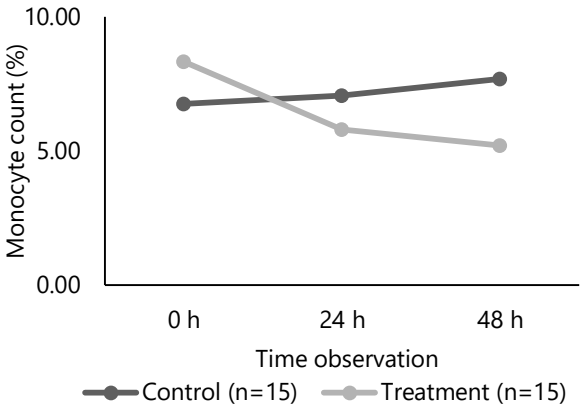


**Figure 1.** The trend of the mean monocyte count in the control and treatment groups

Comparison of the monocyte count at each observation time showed varied results. At the 0-hour observation, the monocytes in the treatment group (8.34%) were higher than the control group (6.75%) (Figure 2a). At the 24th and 48th hour of observation, patients receiving ketamine therapy had lower monocyte count than the control group (Figures 2b and 2c).

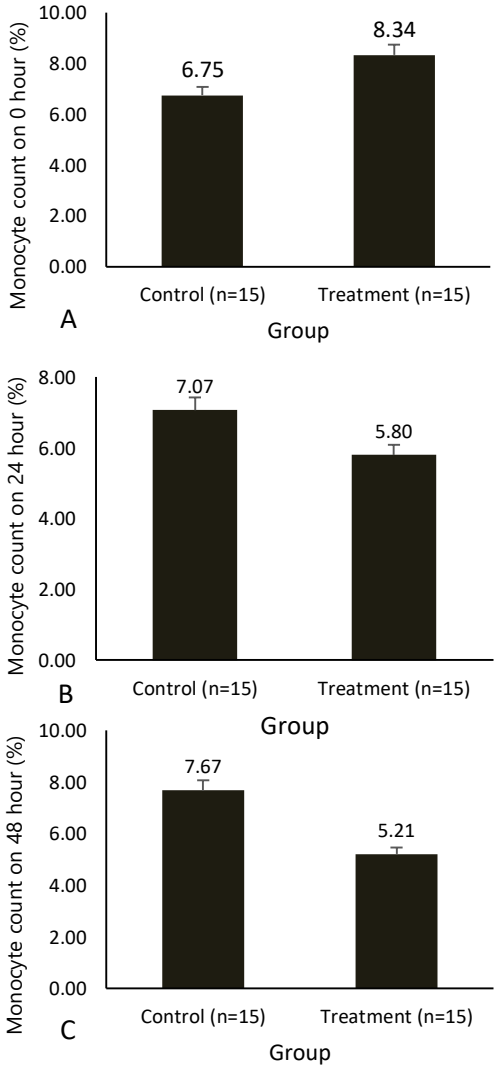


**Figure 2.** Monocyte count each observation time. The treatment group showed a lower monocyte count. A)

examination on 0 h after treatment, B) on 24 h after treatment, C) 48 h after treatment

## DISCUSSION

This study found that the administration of ketamine in sepsis patients shows a decrease in the monocyte count at the 24th and 48th hours of observation. This is in accordance with research by Cruz et al.[11] that ketamine has a role as an anti-inflammatory against endothelial cells experiencing sepsis. Monocytes and other circulating innate immune cells are the earliest cells to recognize and against pathogens. Monocytes have an important role in sepsis and septic shock and have been studied as a potential diagnostic marker. A study conducted by Kohoutková et.al[12] in 24 patients who experienced septic shock found a significantly high monocyte count compared to patients who did not experience shock and obtained a higher mortality rate. This parameter is significantly associated with different levels of the pro-inflammatory cytokines, monocyte chemoattractant protein-1 (MCP-1), Interleukin (IL-6, IL-8, IL-10, and IL-18), as well as with helper T cells.

In a study conducted by Jin and Sang[13] which compared the validity of the monocyte count with C-reactive protein (CRP) levels and procalcitonin levels as a diagnostic marker of sepsis, it was found that an increased monocyte count (using a cut-off > 700/µl) had a sensitivity 77.8% and a specificity of 74.6% compared to CRP with sensitivity of 83.3% and a specificity of 52.5%. Procalcitonin with sensitivity value of 94.4% and a specificity of 72% become the best diagnostic parameter for diagnosing sepsis. However, an increase in the number of monocytes also shows a poor outcome in septic patients.[14] Their study found a relationship between the number of monocytes with mortality, the degree of bacteremia and organ dysfunction. This study also evaluated the number of monocytes when the patient was still in the pre-morbid stage until the occurrence of sepsis including the occurrence of septic shock. The number of monocytes in sepsis may differ depending on the stage of sepsis, but an increase in monocytes may be a sign of a more severe degree of disease. This study found that patients with monocytosis > 750/µL or > 8% showed higher levels of bacteremia, longer use of mechanical ventilation and greater mortality.

In the in-vitro study, experimental animals and humans have found the anti-inflammatory effects of ketamine. Ketamine has an effect on inflammation by precipitating apoptosis in inflammatory cells. This active process involves several cellular mechanisms. It is acquired by apoptosis and or exit from the tissue. Ketamine decreases inflammatory cell release of the pro-inflammatory cytokine TNF-α, the primary apoptotic pathway activator. This is another example of the role of ketamine as an inflammatory regulator.[15]

Experimental and clinical studies show that ketamine has anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines, such as TNF-α and IL-6. In addition, there is increasing evidence that early administration of ketamine reduces mortality in experimental models of sepsis.[16] Research shows that ketamine increases the survival of mice exposed to *E. coli*-induce sepsis by inhibiting the inflammatory cascade, as indicated by a decrease in pro-inflammatory cytokines IL-6. Research also shows that ketamine given immediately after sepsis significantly improves survival by inhibiting the inflammatory cascade represented by a decrease in IL-6 levels.[11] In this study, it was found in the control group (patients who did not receive continuous ketamine) experienced an increase in the monocyte count until the 48th hour of observation. In accordance with the pathophysiological theory of sepsis, there is an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines in the cytokine storm.[17] The presence of excessive systemic inflammation or commonly called a cytokine storm correlates with lymphocytopenia and is a hallmark of severe disease.[18] Theories related to the patient's genetic factors state that sepsis occurs due to a primary immune response to infection and injury in the form of uncontrolled hyper-inflammation due to the failure of innate immune system regulation against pathogens.[19] Another mechanism for the occurrence of sepsis that has been studied is the failure of the immune system, including the formation of immunosuppressive condition and loss of delayed hypersensitivity causing the body to lose its ability to destroy the infection and cause a sustained increase in inflammatory mediators.[20]

In this study, one study sample was excluded after the administration of ketamine at a dose of 0.3 mg/kg body weight for 24 hours due to the side effects of hypersalivation. This effect of ketamine is due to the action of ketamine which is also caused by agonist effects on α and β adrenergic receptors, antagonistic effects on muscarinic receptors in the central nervous system, and agonist effects on σ receptors.[21] However, in a study conducted by Heinz and Geelhood[22] it was found that only 11.4% of patients given ketamine at a dose of 2-2.5 mg/kg experienced side effects of hypersalivation.

In this study, ketamine was used at a continuous dose of 0.3 mg/kg/hour and was considered a safe sub-anesthetic dose and had an anti-inflammatory effect. The study by Groetzinger et.al[23] used continuous ketamine infusion for additional sedation in a mechanically ventilated adult population, targeting light sedation; ketamine was infused at a median initial dose of 1.6-4.2 µg/kg/minute (0.1-0.3 mg/kg/hour) for a median of 2.8 days. The maximum dose of ketamine in individual patients with adverse drug reactions (such as tachyarrhythmias) ranges from 2.08-20 µg/kg/min, necessitating discontinuation of the infusion. Ketamine at a dose of 0.15 mg – 0.3 mg/kg in surgical patients and experimental animals with repeated doses has been shown to reduce levels of the pro-inflammatory cytokines TNFα, IL -6 and IL -8. [24,25]

Ketamine acts at different levels of inflammation, interacting with inflammatory cells, cytokines production and other inflammatory mediators. The immune-inhibitory effect of ketamine has recently been found to be part of the transcriptional inhibition of activator protein-1 factor-1 and nuclear factor-kappa B (NF-κβ), which regulate the production of several inflammatory mediators. In the in-vitro study, a sub-dose of ketamine decreased TNF-α and IL-6 in mice induced into sepsis.[11] In this study, we only measure the monocyte count. To explain the broad range effect of the ketamine effect in immunosuppression in sepsis, further research can be conducted to examine other immunocompetent cells related to sepsis pathogenesis.

## CONCLUSION

Administration of ketamine at a dose of 0.3 mg/kg/hour in septic patients in the ICU decreased the monocyte count compared to the control. The ability of ketamine to reduce the number of monocytes is expected to be a therapeutic option in sepsis management.

## ACKNOWLEDGMENT

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## CONFLICT OF INTEREST

The author declares there is no conflict of interest.

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