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Melatonin prevented the elevation of leukocyte count and the decreased of hematocrit levels in burn-induced Wistar Rats

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ABSTRACT

Background: Burns are commonly caused by thermal injuries that are often encountered in everyday life. Burns may cause tissue damage and tissue infection. Melatonin, a hormone that acts as an antioxidant and anti-inflammatory, can be used as a supportive therapy in patients with burns by preventing excess tissue damage, decreasing inflammatory response, and preventing extreme leukocyte increase. The study aims to investigate the effects of melatonin supplementation on leukocyte count and hematocrit levels in male Wistar rats with burns injury.
Method: This was an experimental animal study with randomized control group design. A total of twelve healthy male Wistar rats were randomized and divided into two groups. All Wistar rats were induced with 30% burns injuries area. The melatonin group was intraperitoneally administered with melatonin at 0, 8, and 16 hours after treatment, while the control group was administered with placebo (aquadest) with similar method. Leukocyte count and hematocrit levels were measured by taking retroorbital venous blood at 0, 3, and 24 hours after treatment. Data were analyzed with Paired t-Test, Independent t-Test, Mann-Whitney, or Wilcoxon test depend on their normality.
Results: There was a higher leukocyte count in control group compared to melatonin group at 3 hours after treatment (T3) (p=0.050), but not at 0 hours after treatment (T0) and at 24 hours after treatment (T24) (p>0.05). There was increased leukocyte count in both melatonin and control groups in T3 in comparison with T0, however the increment was steeper in control group compared to melatonin group. There were no significant differences in hematocrit levels between the melatonin and control groups in T0, T3, and T24 (p>0.05). There was a steeper increased hematocrit levels in the control group than the melatonin group after T24, although it was not statistically significant.
Conclusion: Melatonin might have role in preventing a steeper rise of leukocyte count and hematocrit levels in burns injury. If confirmed by further studies, melatonin might be potential for adjuvant management in burns.

Keywords: Burns injury, leukocyte, hematocrit, melatonin.
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INTRODUCTION

Burns are tissue damage or loss caused by heat (fire, hot fluids/fat, steam), radiation, electricity, or chemistry.[1] There were 300,000 of 11 million people who died from burns globally.[2] Based on Indonesian Basic Health Research, the prevalence of burns in Indonesia was 0.7%, where the highest prevalence was in the provinces of Nangroe Aceh Darussalam and Riau Islands that was at 3.8%.[3] The mortality rate due to burns in Indonesia was still relatively high, around 40%, which was resulted from severe burns.[3] In 2013 to 2015, Indonesia's national referral burn center in Cipto Mangunkusumo Hospital received 414 burns subjects in whom 68.6% subjects were >18 years old and 31.4% were ≤18 years old. The highest proportion of burn incidents or admission was from children 1 to 4 years old age group.[4] The overall mortality rate in burns patients was 24%.[4]

Burns can cause necrosis of the largest organ, the skin.[1] Skin is one of the body's immune mechanism. As a consequence, infection is one of the significant problems in surviving burns patients. Infection begins with bacteria colonization of which has significant impacts on the degree of morbidity, mortality and health costs.[1,5] In addition, burns can cause severe emotional and psychological distress due to disability and death. Burn itself is classified into three degrees based on its severity, namely grade I, degree II, and degree III.[1,6]

Current burns managements have made progress resulting in a reduction in mortality from burns. Burns management is divided into three (3) phases, namely the emergency phase: to prevent hypovolemic shock and maintain vital organ functions, the severe wound management phase, and the acute phase: to overcome infection, wound care, wound closure, pain

management and physical therapy.[1,5]

Burns frequently elicit systemic inflammatory response syndromes (SIRS) and septic shock. Meanwhile, receptors in the cytoplasm recognize bacterial peptidoglycans and/or nucleic acids. When bacterial ligands engage the receptors, these receptors stimulate macrophages to produce tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6. These three pro-inflammatory cytokines produce a systemic inflammatory response which is characteristic of early sepsis.[7,8] The immune response in burns is pro-inflammatory that is then balanced with an anti-inflammatory to maintain homeostasis and to restore physiological function. The immune response may increase pro-inflammatory cytokines, such as IL-1 and TNF-α, and leukocytes.[1,8] The increase of leukocytes is to combat infection in the body.[6] Meanwhile, in the acute phase, burns may also induce elevated hematocrit that is commonly caused by hemoconcentration resulting from fluid loss. After the fluid balance has been restored, lowered hematocrit levels are found secondary to dilution. Over the first week after injury, hemoglobin and hematocrit could be decreased. This decrease was due to loss of red blood cells.[1,9]

Melatonin, a neurohormone in humans and animals, is synthesized by the pineal gland and is usually secreted at night or dark environments.[10] Melatonin has anti-inflammatory, antioxidant, analgesic, hypnotic, chronobiotic, antihypertensive, and immunological effects.[10-12] Melatonin was also thought to be used as adjunctive therapy in burns.[13,14] This is because melatonin can inhibit adhesion molecules and pro-inflammatory cytokines thus inhibit their infiltration into the damaged tissue and prevent more severe burns damage.[14] However, there was still limited studies on the effect of melatonin on leukocytes and hematocrit levels in Wistar burn rats. This study was to know the impact of melatonin on leukocyte count and hematocrit levels in Wistar rats' burn model.

METHODS

This was an experimental animal study with a randomized control group design.

Table 1. Comparison of leukocyte levels between melatonin group and control group.

Leukocyte Count (/ mm³)	Group		*p*
	Control	Melatonin	
T0	6.200 ± 3.240; 6.600 (2.000 – 10.600)	6.300 ± 1.920; 7.400 (6.600 – 11.200)	0.274[a]
T3	9.400 ± 1.420; 9.500 (4.500 – 8.000)	8.200 ± 1.160; 9.200 (8.400 – 11.100)	0.050[a*]
T24	6.200 ± 1.920; 6.100 (3.200 – 8.100)	5.900 ± 800; 6.100 (5.200 – 7.000)	0.663[a]
T0–T3	p=0.035[b*]	p=0.039[b*]	
T0–T24	p=0.627[b]	p=0.536[b]	
T3–T24	p=0.031[b*]	p=0.027[b*]	

Abbreviation: Data was shown as mean ± SD; median (min–max) value; Time 0 hour since treatment (T0); Time 3 hours since treatment (T3), Time 24 hours since treatment (T24); *Significant (p<0.05); [a]Independent t-Test; [b]Paired t-Test.

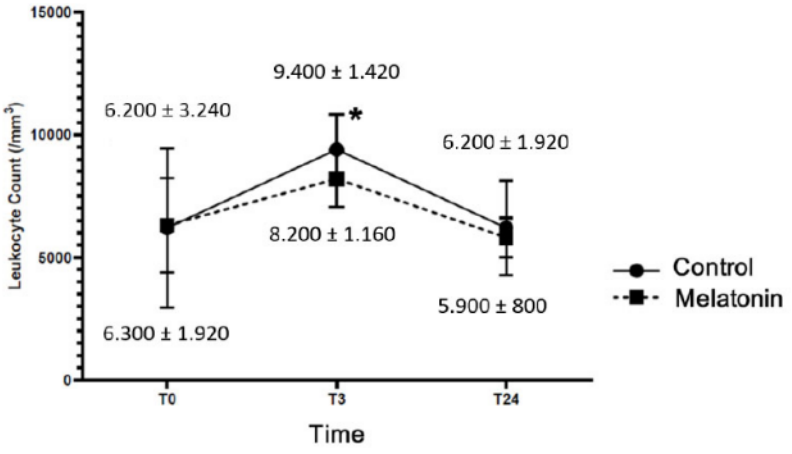

Figure 1. Leukocyte count in melatonin group and control group at 0 hour after treatment (T0), three hours after treatment (T3), and twenty-four hours after treatment (T24). *p<0.05 was considered as statistically significant between control group vs melatonin group.

Twelve healthy male Wistar rats with age range of 2–3 months and body weight range of 200–250 g were used as study subjects. The experiment was carried out for 8 days, divided into 7 days of adaptation period and 1 day of treatment period. They were lived in controlled environment with 12-hours light/dark cycles. All animals were fed with standard pellet diet and water *ad libitum*. All animals were fasting for 12 hours before experimental burn-injury, but were still allowed to drink water.

Experimental animals were divided into two groups, namely (1) Melatonin group (X_M) and (2) the control group (X_c). General anesthesia was performed using thiopental intraperitoneally. Thiopental dose was 0.54 mg/200 g Wistar rat or 30 mg/kg body weight in humans after dose conversion. Each rat received 30% burns of the body surface area or third-degree burns by using a hot metal rod heated in a hot boiling water (90°C). It was applied on the backs of all Wistar rats for 10 seconds. Immediate resuscitation

Table 2. Comparison of Hematocrit Levels between Melatonin Group and Control Group.

Hematocrit Levels (%)	Group		*p*
	Control	Melatonin	
T0	52.8 ± 4.54; 50.6 (47.8 – 57.8)	53.3 ± 5.71; 51.4 (49.2 – 63.0)	0.887[a]
T3	53.7 ± 13.57; 49.3 (45.3 – 77.7)	49.8 ± 1.67; 49.9 (47.5 – 52.0)	0.754[c]
T24	59.8 ± 2.13; 59.1 (57.9 – 62.9)	54.6 ± 4.79; 51.9 (50.7 – 61.6)	0.058[a]
T0–T3	*p*=0.893[d]	*p*=0.345[d]	
T0–T24	*p*=0.061[b]	*p*=0.729[b]	
T3–T24	*p*=0.500[d]	*p*=0.080[d]	

Abbreviation: Data was shown as mean ± SD; median (min–max) value; Time 0 hour since treatment (T0); Time 3 hours since treatment (T3); Time 24 hours since treatment (T24); *Significantly different if $p<0.05$; [a]Independent *t*-Test; [b]Paired *t*-Test; [c]Mann-Whitney test; [d]Wilcoxon test.

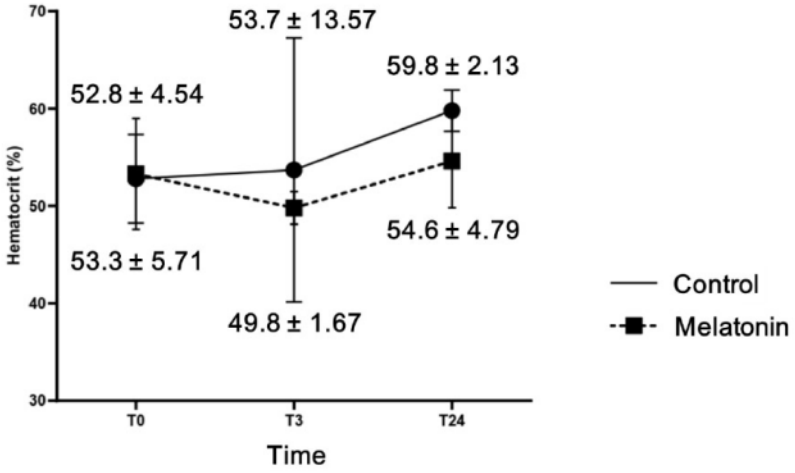

Figure 2. Hematocrit levels in melatonin group and control group at 0 hour after treatment (T0), three hours after treatment (T3), and twenty-four hours after treatment (T24).

with physiological saline (0.18 mg / 200 g Wistar rat or 10 mg/kg body weight in human after dose conversion of 0.018) was performed to all rats.

The melatonin group was administered with melatonin (Melatonin M5250, Sigma-Aldrich, Darmstadt, Germany) intraperitoneally at 0, 8, and 16 hours after burns injury, while the control group was administered with placebo (aquadest) in the same method. Melatonin dose was 0.18 mg / 200 g Wistar rat or 10 mg/kg body weight in human after dose conversion of 0.018.

Blood sample was drawn from retro-orbital venous blood at 0, 3, and 24 hours after treatment. Measurement of leukocyte and hematocrit levels was carried out using automatic hematology analyzer. Data were descriptively analyzed to determine mean, standard deviation, and median. Normality test was performed with Shapiro-Wilk test. Data were analyzed with Paired t-test and Independent t-test due normally distributed. Ethical clearance for animal conduct has been received from ethical committee of Faculty of Medicine, Diponegoro University.

RESULTS

Effect of melatonin in leukocyte levels

Table 1 showed that there was significant difference in leukocyte count between melatonin group and control group in 3 hours after treatment (T3) (p=0.050), but not in 0 hour after treatment (T0) (p=0.274) and in 24 hours after treatment (T24) (p=0.663). We found that there were slightly increased leukocyte count in both melatonin and control groups in T3 in comparison with T0, however the increment was steeper in control group compared to melatonin group (Table 1, Figure 1). It seemed that melatonin could prevent a rise of leukocyte count until 3 hours after treatment in comparison with control.

Effect of melatonin in hematocrit levels

Table 2 showed that there were no significant differences in hematocrit levels between melatonin group and control group in 0 hour after treatment (T0) (p=0.887), 3 hours after treatment (T3) (p=0.754), and in 24 hours after treatment (T24) (p=0.058). We found that there were slightly steeper increased hematocrit levels in the control group after T24 compared to T0. However the increment was steeper in control group compared to melatonin group, although it was not statistically significant (Table 2, Figure 2). It seemed that melatonin might have a role in preventing a steeper rise of hematocrit levels 24 hours after treatment compared to control.

DISCUSSION

Burns are tissue damage that can be caused by hot liquids, contact with hot objects, chemicals, electric currents, fire, and hot steam.[2,4,6] Burns can trigger local and systemic reactions, causing the victim to suffer or even die.[1,5,6,8,15] Infection can occur in large burns, so that bacterial colonies will occupy the damaged tissue and cause increased leukocyte

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production.[8,9] Current technology and science have increased management in treating burns. The high morbidity and mortality of burns have encouraged researchs on main and adjuvant therapies that might prevent complications from burns including melatonin.[10-14,16]

Leukocytes are produced by bone marrow in which there will be an increase if there is inflamed tissue or bacterial contamination or pathogens that secrete immunomodulatory agents. Leukocytes are normal at a number of 5000-9000 / mm^3, and high at a number of more than 9000/mm^3. The increase of leukocytes indicates the activation of self-defense and the immune system when there is an inflamed tissue that causes an inflammatory process.[17,18]

Our study showed a higher leukocyte count in the control group than the melatonin group in 3 hours after treatment (T3). We found that there was increased leukocyte count in both control and melatonin groups in T3 in comparison with T0, however the increment was steeper in control group compared to melatonin group. It seemed that melatonin could prevent a rise of leukocyte count until 3 hours after treatment in comparison with control.

We also showed that there were slightly steeper increased hematocrit levels in the control group after T24 compared to T0. The increment was more vertical in the control group compared to the melatonin group, although there were no significant differences in hematocrit levels between the melatonin and control groups in each timeline. Our study revealed that melatonin might have a role in preventing a steeper rise of hematocrit levels in 24 hours after treatment compared to control.

Melatonin is a versatile neurohormone molecule synthesized by the pineal gland which increases resistance to infection or inflammation.[10-12,19] In thermal injury, melatonin might also protect body as an antioxidant and good immunity enhancer as in other reported cases.[13,14,20] Melatonin is a hormone that has been developed as a supportive therapy in burn patients.[11,13]

Maldonado et al. reviewed that melatonin could have role as a supportive pharmacologic agent in burn patients including as a scavenger of both oxygen and nitrogen-based reactants, a stimulator of the activities of anti-oxidative enzymes, an inhibitor of pro-inflammatory cytokines, an inhibitor of adhesion molecules, inhibitor in the toxicity of the drugs used in protocols to treat thermal injury, and chronobiotic effects.[13] Hence it could prevent oxidative damage, reduce inflammatory cytokine levels and also mitochondrial dysfunction.

Sener et al. showed that severe skin scald injury (30% of total body surface area as in our study) caused a significant decrease in glutathione (GSH) level, significant increases in malondialdehyde (MDA) and protein oxidation (PO) levels, and myeloperoxidase (MPO) activity at post-burn 3 and 24 h, while treatment with melatonin (10 mg/kg) prevented oxidative damage by elevating the reduced GSH levels, decreasing MDA and PO levels as well as MPO activity.[14]

In line to our study, Lin et al. evaluated the effect of melatonin in heatstroke rats and showed that melatonin attenuated inflammatory mediators and systemic inflammation response molecules like soluble intercellular and lesion molecule-1, E-selectin, TNF-α, IL-1β, and IL-6; promoted plasma levels of an anti-inflammatory cytokine IL-10; reduced infiltration of polymorphonuclear (PMN) neutrophils; and reduced toxic oxidizing radicals in plasma-like nitric oxide metabolites and hydroxyl radicals.[16] We hypothesized that our findings in which melatonin could ameliorate leukocyte count and hematocrit levels, might proceed through those similar mechanisms as alleviating inflammation and oxidizing radicals.

Lin et al. also showed that melatonin could promote the survival time to fourfold compared to control group; could attenuate hyperthermia, hypotension and hypothalamic ischemia and hypoxia; and could ameliorate hepatic and renal dysfunction biomarkers like creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase. They revealed that melatonin could be a novel treatment of heat-stroke in the early stage.[16]

Our present study was similar to study from Wicaksono et al. which showed that melatonin could prevent the elevation of leukocyte count and the decrease of platelet count in Wistar rats endotoxicosis model.[21] Wicaksono et al. also showed that melatonin could prevent excess increase of lactate and random blood glucose levels in Wistar rats endotoxicosis model.[22]

A study from Yavuz et al. showed that melatonin had therapeutic benefits in Candida sepsis in a rat model. They revealed that septic rats showed a higher serum IL-6, TNF-α, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin levels than those of controls, while melatonin could reduce IL-6, TNF-α and adhesion molecules levels and shorten the improvement time in animals with Candida sepsis.[23]

Numerous data supported the idea that thermal injury produced depressed immunologic functions, such as reversal of T-helper/suppressor cell ratio, decreased neutrophil and B-cell functions. Lymphocytopenia also observed in severely injured patients that were the result of the overexpression of adhesion molecules on the T-cell surface. In severe burns, the overall number of lymphocytes gradually increased, with a concomitant decrease in double-positive CD4+ CD8+ lymphocytes.[13] Meanwhile, melatonin could reduce neutrophil levels and block the synthesis of molecules adhesion in burns and prevent further tissue damage.[13] In line to those findings, our study showed that melatonin could reduce the leukocyte count levels. However we did not classify the impact of burns to each leukocyte type and the surface markers.

This study's limitation was that we could not control the effect of stress and organ damage in burns rats to the study results. Therefore, it is necessary to carry out further studies with different melatonin exposures, with different melatonin doses, with different markers analyzed and with more study subjects. We need to do further studies that determine the level of organ damage or stress due to burns by examining chemical blood markers. In addition, clinical studies might be needed regarding the safe dosage of melatonin in its use as an antioxidant and anti-inflammatory.

CONCLUSIONS

Melatonin might have role in preventing a steeper rise of leukocyte count and hematocrit levels in burns injury. If confirmed by further studies, melatonin might be potential for adjuvant management in burns.

FUNDING

This study doesn't receive any specific grant from the government or any private sector.

CONFLICT OF INTEREST

All author declares there is no conflict of interest regarding this article's publication.

ETHICAL CONSIDERATION

This study has been approved by the Ethical Committee Faculty of Medicine, Universitas Diponegoro, with ethical clearance reference number: No. 40/EC/H/FK-UNDIP/V/2020. All study protocol in accordance with The Universal Declaration of Animal Welfare.

AUTHOR CONTRIBUTION

MFK and SAW conducted the study. SBU and SAW involved in concepting, designing and supervising the manuscript. SAW, FF and EK analyzed the data. All authors prepared the manuscript and agreed for this final version of manuscript to be submitted to this journal.

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PAGE 4

PAGE 5