JMCH Journal of Maternal and Child Health (2023), 09(05): 787-793
Masters Program in Public Health, Universitas Sebelas Maret

Research
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Efficacy of Melatonin in Neonatal Sepsis with Respiratory Distress: A Randomized Controlled Study

Dwi Hidayah[1)], Nur Irfani Agita Suwarna[2)]

[1)]Department of Pediatric, Faculty of Medicine, Universitas Sebelas Maret
[2)]Universitas Sebelas Maret Hospital, Indonesia

Received: 09 August 2024; Accepted: 08 September 2024; Available online: 16 September 2024

ABSTRACT

Background: Neonatal sepsis is a significant condition worldwide, contributing to high morbidity and mortality, especially in developing countries such as Indonesia. Neonatal sepsis can rapidly progress to respiratory distress. Melatonin, an effective antioxidant and free radical scavenger, may be an adjuvant therapy. This study aimed to evaluate the efficacy of melatonin in neonatal sepsis with respiratory distress.
Subjects and Method: A double-blind randomized controlled study was conducted on 42 neonatal sepsis with respiratory distress diagnosed with clinical and laboratory criteria. The subjects were randomly allocated into treatment and control groups, receiving a single dose of oral melatonin 20 mg and a placebo, respectively. The dependent variables were improvement of suplementation in oxygenation and ventilator, outcome, and hospital length of stay. The independent variables was suplementation melatonin The oxygen supplementation and ventilation support were measured at baseline and 72 hours after therapy. We analyzed all data with SPSS 25 using independent t test and determined the significance level at $p < 0.050$.
Results: Seven of the 21 subjects in the treatment group experienced decreased oxygen supplementation and ventilation support, which was statistically significant ($p = 0.009$). While the outcome for both groups was the same proportion, it was statistically not significant ($p = 1.000$).
Conclusion: Melatonin administration significantly decreased oxygen supplementation and ventilation support.

Keywords: melatonin, neonatal sepsis, respiratory distress.

Correspondence:
Dwi Hidayah. Department of Pediatric, Faculty of Medicine, Universitas Sebelas Maret. Jalan Kolonel Sutarto No. 132, Surakarta 57126, Indonesia. Email: dwihidayah_dr2020@staff.uns.ac.id. Mobile: 08122623728.

Cite this as:
Hidayah D, Suwarna NIA (2024). Efficacy of Melatonin in Neonatal Sepsis with Respiratory Distress: A Randomized Controlled Study. *J Matern Child Health*. 09(05): 787-793. https://doi.org/10.26911/thejmch.2024.09.05.03.

BACKGROUND

Neonatal sepsis is a major global cause of death, resulting in over 8 million deaths annually (Dulgani et al., 2017). The mortality rate is 50% or higher in developing countries, including Indonesia. Severe sepsis can lead to complications such as respiratory distress, which have high mortality rates (Gitto et al., 2011).

Because of the consumption of oxygen

during first resuscitation and the underdeveloped fetal antioxidant system, newborns are vulnerable to oxidative stress-induced injuries. A vast amount of inflammatory substances and immune cells enter the alveoli and produce a hyaline membrane as a result of the strong inflammatory response brought on by sepsis (Poggi et al., 2018). During acute systemic inflammation, swelling and necrosis of alveolar capillary endothelial cells worsen severe hypoxemia (You et al., 2022). An Adequate oxygen supplementation and ventilation support to prevent hypoxemia could potentially facilitate the recovery of alveolar epithelial damage in respiratory distress. During hospitalization, neonates in need of intensive treatment are subjected to unpleasant stimuli such as invasive and noninvasive ventilation (Cannavò et al., 2022). Pro-inflammatory cytokines are widely known to play a crucial role in initiating and sustaining pain.

Melatonin is a natural indolamine produced in the pineal gland from serotonin hypoxemia (Rieter et al., 2009). Melatonin's analgesic properties appear to be associated with anti-inflammatory and antioxidant actions hypoxemia (Radognaet al., 2010). T Melatonin medication may alleviate pain-related stress and protect the lungs from inflammation and oxidative damage in neonates. Furthermore, melatonin's antioxidant impact appears to reduce lung inflammation, shorten breathing times, and improve lung disease outcomes hypoxemia (Hu et al., 2020).

Melatonin has been used as an adjuvant treatment for premature infants with neonatal sepsis (El-Kabbany et al., 2020; El Frargy et al., 2020; El-Gendy et al., 2018; Hidayah et al., 2024;). Melatonin may have favorable effects on neonatal sepsis, improving clinical outcomes.

SUBJECTS AND METHOD

1. Study Design

This study is a double-blind randomized controlled study with an allocation ratio of 1:1. It used purposive sampling, where subjects who met the inclusion criteria were included and then grouped based on the randomization block 6, which had been created previously and placed in a sealed envelope.

2. Population and Sample

After obtaining informed consent, subjects of appropriate gestational age diagnosed with neonatal sepsis with respiratory distress based on clinical and laboratory standards were documented. We included patients who were diagnosed with high probability sepsis (HPS) or probable sepsis (PRS) based on the sepsis score (Table 1).

3. Study Variables

We excluded neonates with major congenital anomalies of the gastrointestinal tract, continuous vomiting, hypoxic-ischemic encephalopathy (HIE), feeding intolerance, NEC, and septic shock. The enrolled subjects were allocated into 2 groups: treatment and control groups. All subjects were taken from the Neonatal Intensive Care Unit (NICU) of Dr Moewardi Hospital, Surakarta, Indonesia, between April and October 2023.

4. Operational Definition of Variables

Every patient had a history taken, a clinical examination, and laboratory testing. High-sensitivity C-reactive protein (hs-CRP) was quantitatively measured with TMS 50 I, hs-CRP > 0.5 mg/dL was considered the cut-off point. We recorded the administration of oxygen supplementation and ventilation support at baseline and 72 hours after therapy. Improvement was defined when the subject experienced decreased oxygen supplementation and ventilation support.

Table 1. Sepsis score definitions

Sepsis score	Definition
High probable sepsis	Criteria for sepsis include at least 3 clinical symptoms* hs-CRP > 0,5 mg/dL, At least 2 altered serum indicators† Blood culture: positive or negative
Probable sepsis	Less than 3 clinical indications of sepsis* hs-CRP > 0,5 mg/dL, At least 2 additional altered serum indicators† Blood culture: negative
Possible sepsis	Less than 3 clinical indications of sepsis* hs-CRP < 0,5 mg/dL There are less than 2 additional altered serum indicators† Blood culture: negative
No sepsis	There were no sepsis-related clinical symptoms* hs-CRP < 0,5 mg/dL Serum parameters remained unchanged† Blood culture: negative

*Clinical indicators of sepsis include temperature instability, apneic spells, the requirement for supplemental oxygen and ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, and necrotizing enterocolitis.
† Other serum indicators besides CRP include the number of white blood cells (WBC), absolute neutrophil count (ANC), and platelet (PLT) count.

5. Study Instruments

The subjects in the treatment group received antibiotics and a 20 mg single oral dose of powdered melatonin dissolved in 3 ml of distilled water administered via an orogastric tube (OGT), while those in the control group received placebo and antibiotics. The therapy given was based on the standard protocol. The parents gave their informed consent.

6. Data analysis

All data were statistically evaluated using SPSS 25. Quantitative data were presented as mean ± SD, while qualitative data were reported as frequency and percentage. We used independent t-tests to analyze continuous, normally distributed data. For categorical data comparison between groups, we employed a t-test, considering a p-value of less than 0.05 as statistically significant.

7. Research Ethics

It explains ethical issues arising when people are involved as participants in this study. The The study was conducted at Dr. Moewardi Hospital with approval from the hospital's ethics committee 1.657/XII/-HREC/2022.

RESULTS

1. Sample Characteristics

Fifty-one subjects were screened for eligibility, and 9 of them were excluded due to HIE (n = 1), feeding intolerance (n = 5), NEC (n = 1), and septic shock (n = 2). Forty-two subjects met the inclusion criteria and were then allocated into treatment (n = 21) and control groups (n= 21). Regarding gestational age, birth weight, age, sex, and mode of delivery were comparable between the control and treatment groups; there were no differences (p>0.05). The demographic characteristics of patients data continue (Table 2) and data categorical (Table 3).

2. Bivariate Analysis

Table 4 summarizes before and after administering oxygen supplementation and

ventilation support. The use of ventilation was significantly decreased in the treatment group based on the results (p = 0.009). The outcomes of patients in both groups are shown in (Table 5) without significant differences. There were no adverse events to melatonin administration in this study. The comparison of hospital length of stay (days) in both groups (Table 6).

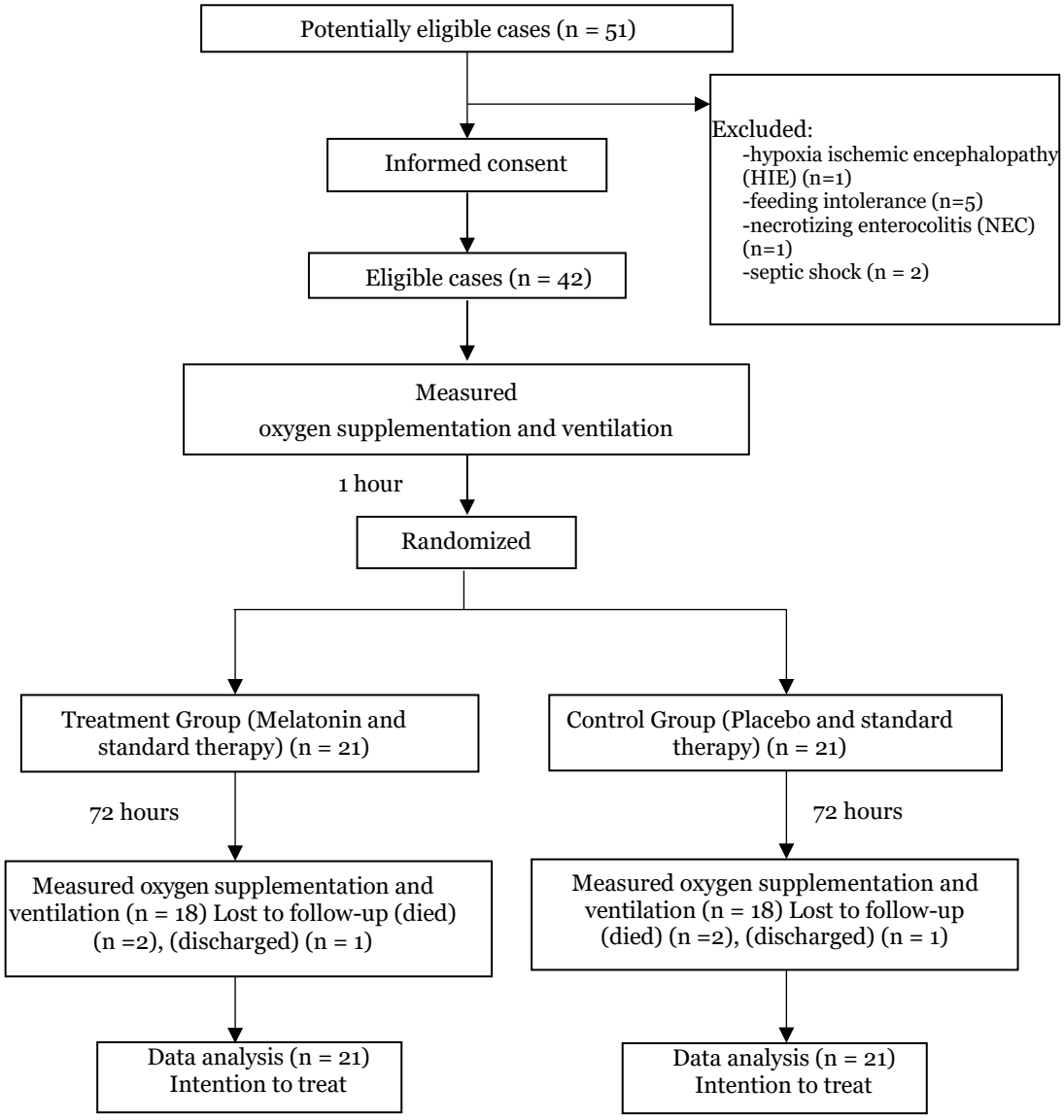

Figure 1. Participant flow-chart

Table 2. Study characteristics data continue

Sample	Control Group Value		Treatment Group Value		p
	Mean	SD	Mean	SD	
PMA (weeks)	30.00	10.2	31.19	7.6	0.650
Gestational Age (weeks)	31.52	2.4	31.28	2.3	0.251
Birth Weight (gram)	11683.80	398.1	1538.80	477.9	0.346
Aged (days)	9.76	7.4	11.95	7.1	0.101

Table 3. Study characteristics data categorical

Sample	Control Group Value (%)		Treatment Group Value (%)		p
	n	%	n	%	
Sex					
Male	12	57.2	12	57.2	1.000
Female	9	42.8	9	42.8	
Mode of Delivery					
Pervaginam	5	23.8	7	33.3	0.495
Perabdominal	16	76.2	14	66.7	

*p<0.05 indicates statistical significance

Table 4. Oxygen supplementation and ventilation support changes

Variable	Before				After			
	Control Group		Treatment Group		Control Group		Treatment Group	
	n	%	n	%	n	%	n	%
Room Air	2	9.5	2	9.5	2	9.5	6	28.6
Nasal Canule	4	19.1	9	42.8	3	14.3	4	19.0
CPAP	7	33.3	0	0	8	38.1	0	0
NIV	6	28.6	3	14.2	6	28.6	2	9.5
VM/PC	2	9.5	7	33.3	2	9.5	9	42.9

CPAP stands for continuous positive airway pressure. NIV for non-invasive ventilation. and VM/PC for ventilation mechanical pressure controlled.

Table 5. Comparison in both groups

Variable	Control Group Value		Treatment Group Value		p
	n	%	n	%	
Improvement					
Improve	0	0	7	25	0.009
Not Improve	21	100	14	75	
Outcome					
Death	12	57.1	12	57.1	1.000
Alive	9	42.9	9	42.9	

Table 6. Comparison of hospital length of stay in both groups

Variable	Control Group Value		Treatment Group Value		p
	Mean	SD	Mean	SD	
Hospital length of stay (days)	20.28	11.2	21.80	11.51	0.693

DISCUSSION

One of the most frequent causes of neonatal morbidity and death over the last few decades has been sepsis which develops within 72 hours of after birth. Furthermore, respiratory distress is associated with significant fatality rates in neonates with sepsis (Kim et al., 2016). Several etiological variables contribute to lung injury in the neonatal period, including genetic, hemodynamic, metabolic, nutritional, mechanical, infectious, and inflammatory causes. All of these activities promote the creation of free radicals, which cause oxidative stress-mediated tissue damage (D'Angelo et al., 2020).

In this study, the administration of melatonin decreased oxygen supplementa-

tion and ventilation statistically significantly. Melatonin has been shown in several studies to possess broad-spectrum antioxidant effects. Melatonin administered at night decreased interstitial fibrosis and alveolar count. Gitto et al. (2011) conducted a study comparing preterm newborns who were treated with melatonin to those who were not. They evaluated the plasma concentration before and after 24, 72 hours, and 7 days of mechanical ventilation. They found that the serum levels of pro-inflammatory cytokines were similar before endotracheal intubation, but significantly lower after. The research demonstrated that melatonin administration reduced proinflammatory cytokines and improved clinical outcomes. Additionally, melatonin was found to scavenge free radicals and increase the levels of antioxidant enzymes (Gitto et al., 2011).

We found no differences in the outcomes when comparing the treatment and control groups. This is consistent with the research by El Gendy et al, which showed no statistically significant difference in outcomes. There were no melatonin-related adverse effects reported in our patients. Melatonin seems to be safe as no negative effects have been documented.

The study has some weaknesses, including a limited sample size, lack of long-term follow-up of the patients, and absence of paraclinical data on proinflammatory cytokines. Additionally, well-designed investigations are necessary before clear consensus and guidelines can be established. Future research is required to determine the best melatonin dose and timing for optimal clinical outcomes.

In conclusion, our study found that using melatonin as an additional treatment in neonatal sepsis with respiratory distress significantly reduced the need for oxygen supplementation and ventilation support. These findings suggest that melatonin could be used as a preventive and therapeutic antioxidant in treating neonatal sepsis.

AUTHOR CONTRIBUTION

Dwi Hidayah and Nur Irfani Agita Suwarna played a role starting from determining the idea. writing the article. data analysis. to editing.

FUNDING AND SPONSORSHIP

The authors did not receive any particular grants from governmental. commercial. or non-profit funding agencies.

ACKNOWLEDGEMENT

We appreciate the NICU nurses who were involved in neonatal care.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

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