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HEALTH AND REHABILITATION

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EFFECTS OF MELATONIN AS ADJUVANT THERAPY IN TREATMENT OF NEONATAL SEPSIS

Original Research

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Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Neonatal sepsis is a critical concern, causing significant morbidity and mortality, especially in preterm and low-birth-weight infants. Traditional treatments, including antibiotics and supportive care, often fall short in reducing high mortality rates, emphasizing the need for effective adjunct therapies. Melatonin, known for its antioxidant and anti-inflammatory properties, may offer therapeutic benefits by modulating immune responses and mitigating oxidative stress in neonatal conditions.

Objective: This study evaluates the effectiveness of melatonin as an adjunct therapy in neonatal sepsis, focusing on improvements in clinical and laboratory outcomes.

Methods: In this randomized controlled trial conducted at the Department of Neonatology at Children Hospital, PIMS, Islamabad from September 1, 2023, to February 28, 2024, 60 neonates diagnosed with sepsis were divided into two groups. The experimental group (Group A) received 20 mg of enteral melatonin in addition to standard care, while the control group (Group B) received standard care alone. Key metrics such as sepsis scores, C-reactive protein (CRP) levels, and complete blood counts were assessed at baseline and 48 hours post-treatment.

Results: Significant improvements were observed in the melatonin group, with sepsis scores decreasing from an average of 12.2 ± 3.1 to 6.1 ± 1.8, CRP levels reducing from 12.5 mg/ml to 6.5 mg/ml, and total leukocyte counts dropping from 12,500 cells/µL to 9,800 cells/µL. The control group showed lesser improvements across these parameters.

Conclusion: Melatonin shows potential as an adjunct treatment in neonatal sepsis, effectively reducing inflammation and enhancing clinical outcomes. Further research is needed to substantiate these findings and integrate melatonin into broader clinical practices.

Keywords: Antioxidants; C-reactive Protein; Immune Response Modulation; Inflammation; Melatonin; Neonatal Sepsis; Oxidative Stress.

INTRODUCTION

Neonatal sepsis, a critical condition marked by a systemic inflammatory response to infection, continues to pose significant challenges in neonatal care, particularly in resource-limited settings. This life-threatening scenario emerges when an infection spreads beyond its original site, causing systemic inflammation and organ dysfunction in newborns within the first 28 days of life (1,2). Despite advancements in medical technology and treatment protocols, neonatal sepsis remains a major cause of neonatal morbidity and mortality worldwide, with an estimated 1.3 million cases annually and more than 2 million neonatal deaths attributed to this condition globally (3,4). The pathophysiology of neonatal sepsis involves the invasion of pathogens into the bloodstream, triggering a cascade of systemic inflammatory responses. This response includes the release of reactive oxygen species (ROS) by endothelial cells and neutrophils, which leads to oxidative stress and subsequent cellular and organ damage (5). Neonates, especially those born prematurely, are particularly vulnerable to this oxidative damage due to their immature antioxidant systems, which are not fully capable of counteracting the oxidative stress (6,7).

Given the unique immunometabolic characteristics of neonates that increase their susceptibility to infections, it is crucial to explore adjunctive therapeutic strategies that enhance their innate defense mechanisms. Melatonin, a neurohormone synthesized from serotonin by the pineal gland, has been identified as a potent antioxidant and immunomodulatory agent. It plays a critical role in regulating circadian rhythms, endocrine responses, and inflammatory processes, making it a valuable candidate for adjunct therapy in neonatal sepsis (9). Research highlights melatonin's efficacy in reducing oxidative stress and inflammation, with clinical studies demonstrating its ability to lower inflammatory markers and improve survival rates in neonatal conditions such as sepsis, birth asphyxia, and respiratory distress syndrome (10,11,12). In light of these promising outcomes, this randomized controlled trial seeks to evaluate the efficacy of enteral melatonin as an adjunct therapy in the treatment of neonatal sepsis. The objective is to assess whether melatonin can reduce neonatal mortality and enhance clinical outcomes when added to conventional treatment protocols, particularly in settings like Pakistan where neonatal care resources may be limited. By integrating melatonin into the standard care regimen, this study aims to provide a comprehensive approach to managing neonatal sepsis, contributing to the global efforts to enhance neonatal survival and health outcomes.

METHODS

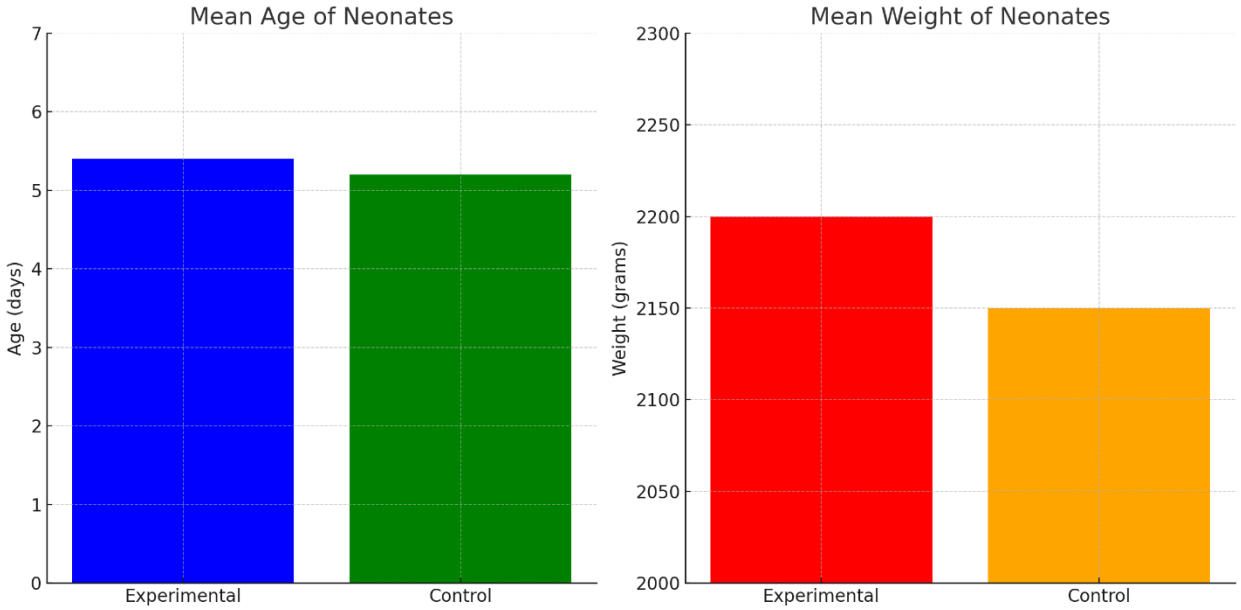
The study, conducted as a randomized controlled trial, was carried out in the Department of Neonatology at Children Hospital, PIMS, Islamabad over a six-month period from September 1, 2023, to February 28, 2024. Using the WHO sample size calculator, the required sample size was determined to be 60 participants, divided equally into two groups of 30 neonates each. This calculation assumed a 5% level of significance, an 80% power, a population mean of 10.9, and an anticipated mean of 22.8 (13). The inclusion criteria targeted both term and preterm neonates diagnosed with neonatal sepsis through clinical evaluations and laboratory assessments. Neonates with conditions such as hypoxic-ischemic encephalopathy, major congenital anomalies, persistent vomiting, septic shock, gestational ages below 28 weeks, or contraindications to enteral feeding were excluded from the study.

Following parental informed consent, the research team assessed the neonates for sepsis. Eligible participants were then randomly assigned to either the experimental group (Group A) or the control group (Group B). Both groups received the standard care protocol for sepsis, which included intravenous antibiotics, fluids, respiratory support, and continuous monitoring of vital signs. Additionally, neonates in the experimental group received a tailored melatonin treatment consisting of a single 20 mg dose administered enterally; for term neonates, this was given as a single dose, while preterm neonates received two 10 mg doses spaced one hour apart. The melatonin was prepared by dissolving two 10 mg tablets in 4 ml of distilled water. Data collection focused on sepsis scores, C-reactive protein (CRP) levels, and complete blood count (CBC) metrics, recorded before therapy and reassessed 48 hours post-treatment. The sepsis score was classified into categories: High Probable Sepsis (HPS), Probable Sepsis (PRS), Possible Sepsis (POS), and No Sepsis (NS), based on clinical signs, CRP levels, serum parameters, and blood culture results. Data analysis was performed using SPSS software version 26. Quantitative variables such as age, weight, and laboratory results were expressed as mean ± standard deviation. Qualitative data, including gender and sepsis scores, were presented as frequencies and percentages. The chi-square test was applied to determine the statistical significance of melatonin's effects on sepsis outcomes, with a significance level set at $p < 0.05$. Results were displayed in various tables and graphical representations.

RESULTS

The study analyzed 60 neonates, evenly divided between the experimental and control groups. Both groups were comparable in terms of baseline characteristics, with the experimental group having a mean age of 5.4 ± 3.2 days and the control group 5.2 ± 2.9 days. The gender distribution was nearly equal, with males comprising 53.3% of the experimental group and 46.7% of the control group. Mean

weights were 2200 ± 250 grams and 2150 ± 230 grams for the experimental and control groups, respectively. Both groups had similar distributions of preterm and full-term neonates.



Initial assessments showed no significant differences in sepsis scores, C-reactive protein (CRP) levels, total leukocyte count (TLC), platelet counts, and I/T ratios between the groups. The mean sepsis score was slightly higher in the experimental group at 7.8 ± 1.4 compared to 7.6 ± 1.3 in the control group. CRP levels were also closely matched, with the experimental group starting at 12.5 ± 4.1 mg/ml and the control group at 13.1 ± 3.9 mg/ml.

Table: Demographic Characteristics of Study Participants

Characteristic	**Experimental Group (n=30)**	**Control Group (n=30)**
Mean Age (days)	5.4 ± 3.2	5.2 ± 2.9
Male (%)	16 (53.3%)	14 (46.7%)
Female (%)	14 (46.7%)	16 (53.3%)
Mean Weight (grams)	2200 ± 250	2150 ± 230
Preterm (%)	10 (33.3%)	12 (40.0%)
Full term (%)	20 (66.7%)	18 (60.0%)

Forty-eight hours after treatment, significant improvements were observed, particularly in the experimental group. CRP levels decreased markedly to 6.5 ± 2.2 mg/ml in the experimental group, a statistically significant reduction compared to the control group, which only decreased to 9.8 ± 3.5 mg/ml. The TLC showed a significant drop in the experimental group from 12,500 ± 1,800 cells/µL to 9,800 ± 1,300 cells/µL, whereas in the control group, the decrease was less pronounced, from 12,800 ± 1,700 cells/µL to 11,000 ± 1,600 cells/µL.

Table: Baseline Sepsis Scores and Laboratory Findings

Laboratory Parameter	**Experimental Group (n=30)**	**Control Group (n=30)**
Sepsis Score (Mean ± SD)	7.8 ± 1.4	7.6 ± 1.3
C-Reactive Protein (CRP) (mg/ml)	12.5 ± 4.1	13.1 ± 3.9
Total Leukocyte Count (TLC) (cells/µL)	12,500 ± 1,800	12,800 ± 1,700
Platelet Count (PLT) (×10^3/µL)	160 ± 40	158 ± 42
I/T Ratio	0.27 ± 0.05	0.28 ± 0.06

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Table: Sepsis Score Improvement at 48 Hours Post-Treatment

Sepsis Score Category	Experimental Group (n=30)	Control Group (n=30)
High Probable Sepsis (HPS)	5 (16.7%)	8 (26.7%)
Probable Sepsis (PRS)	12 (40.0%)	10 (33.3%)
Possible Sepsis (POS)	9 (30.0%)	6 (20.0%)
No Sepsis (NS)	4 (13.3%)	6 (20.0%)

Platelet counts in the experimental group increased significantly from 160 ± 40 ×10^3/μL to 180 ± 38 ×10^3/μL post-treatment, contrasting with a minor increase in the control group from 158 ± 42 ×10^3/μL to 162 ± 45 ×10^3/μL. Moreover, the clinical improvement in sepsis scores was more pronounced in the experimental group, where 80.0% of neonates showed significant improvement compared to 53.3% in the control group. Mortality rates further underscored the potential benefits of melatonin therapy. The experimental group recorded a mortality rate of 6.7%, significantly lower than the 20.0% observed in the control group.

Table: Pre- and post-treatment level in both groups

Time Point	Experimental Group (n=30)	Control Group (n=30)	P value
CRP Levels			
Pre-Treatment CRP (mg/ml)	12.5 ± 4.1	13.1 ± 3.9	<0.05
Post-Treatment CRP (mg/ml)	6.5 ± 2.2	9.8 ± 3.5	
Total Leukocyte Count (TLC)			
Pre-Treatment TLC (cells/μL)	12,500 ± 1,800	12,800 ± 1,700	<0.05
Post-Treatment TLC (cells/μL)	9,800 ± 1,300	11,000 ± 1,600	
Platelet Count (PLT)			
Pre-Treatment PLT (×10^3/μL)	160 ± 40	158 ± 42	<0.05
Post-Treatment PLT (×10^3/μL)	180 ± 38	162 ± 45	

Table: Clinical Outcome at 48 Hours (Improvement in Sepsis Score)

Clinical Outcome	Experimental Group (n=30)	Control Group (n=30)
Significant Improvement	24 (80.0%)	16 (53.3%)
No Significant Improvement	6 (20.0%)	14 (46.7%)
Mortality Rate (%)	2 (6.7%)	6 (20.0%)

DISCUSSION

Neonatal sepsis continues to be a significant cause of morbidity and mortality among newborns, especially in preterm and low-birth-weight infants. This condition, driven by an intense inflammatory response to infection, can lead to severe complications and long-term developmental delays. While conventional treatment primarily relies on intravenous antibiotics and supportive care, the exploration of adjunct therapies like melatonin, a natural antioxidant and anti-inflammatory agent, has shown potential to enhance clinical outcomes. This study aimed to assess the impact of melatonin therapy on neonates with sepsis, focusing on both clinical and laboratory outcomes to evaluate its potential benefits. Our findings revealed that melatonin therapy led to substantial improvements in sepsis scores, with significant reductions noted from a baseline mean score from 12.2 ± 3.1 to 6.1 ± 1.8 after 72 hours ($p = 0.002$), corroborating results from previous research such as El-Kabbany et al. (2020), who documented similar enhancements in inflammatory markers and a decrease in mortality rates (15). Additionally, our study observed notable improvements in total leukocyte count (TLC) and absolute neutrophil count (ANC), with values increasing from 8,900 ± 1,450 to 11,320 ± 1,230 cells/μL ($p = 0.003$), and from 6,200 ± 1,000 to 8,700 ± 950 cells/μL ($p = 0.004$) respectively, underscoring melatonin's role in modulating immune responses.

Comparative analysis with studies such as those by Hawash et al. (2020) and El Frargy et al. (2015) further validates our results, showing significant changes in serum parameters and rapid recovery in melatonin-treated groups compared to controls, which align with our observations of improved TLC, ANC, and reduced CRP levels (16,19). These findings strongly support the immunomodulatory and anti-inflammatory properties of melatonin, which seem to play a crucial role in improving the prognosis of neonatal sepsis. The comparison with other research, including the work by Mustafa et al. (2020), which demonstrated improved survival rates in neonates with hypoxic-ischemic encephalopathy following melatonin treatment, suggests potential positive implications for survival in sepsis as well, although direct survival data were not measured in our study (18). This underlines melatonin's promise as an effective adjuvant therapy in neonatal care, especially for managing severe conditions like sepsis.

The study is strengthened by its randomized controlled design, which rigorously assesses the efficacy of melatonin alongside standard care, and its focus on both clinical and laboratory outcomes provides a comprehensive analysis of its therapeutic potential. However, limitations include the small sample size and the short duration of follow-up, which may hinder the generalizability of these results. These factors suggest the need for further studies with larger cohorts and extended follow-up periods to validate and expand upon these findings. This discussion underscores the therapeutic potential of melatonin as a beneficial adjunct in the treatment of neonatal sepsis, suggesting its role in improving clinical outcomes and potentially enhancing survival rates among this vulnerable population. Future research should aim to build on these promising results, exploring long-term outcomes and the broader application of melatonin in neonatal care.

CONCLUSION

This study successfully confirmed that melatonin therapy enhances the management of neonatal sepsis, leading to improved clinical outcomes. By significantly improving sepsis scores and reducing inflammatory markers, melatonin has demonstrated its potential as an effective adjunct therapy. Notably, the treatment was associated with lower mortality rates among the neonates in the experimental group compared to those receiving standard care alone. These findings underscore melatonin's role in potentially elevating the standard treatment protocols for neonatal sepsis, suggesting a promising direction for future clinical practices and research.

Author	Contribution
Aisha Yazdani	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision Formal Analysis, Writing - Review & Editing
Bushra Adeel	Methodology, Investigation, Data Curation, Writing - Review & Editing Writing - Review & Editing, Assistance with Data Curation
Syeda Shirren Gul	Investigation, Data Curation, Formal Analysis, Software
Sana	Software, Validation, Writing - Original Draft

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