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Original Research Article

Role of Inhaled Budesonide in Neonates with Meconium Aspiration Syndrome

Mah Noor[1*], Saima Manzoor[2], Saba Wamiq[2], Asif Javeed[2]

[1]Department of Paediatric Medicine, Ibn-E-Sina Hospital, Multan, Pakistan
[2]Department of Peadiatric Medicine, Multan Medical & Dental College/ Ibn-e-Siena Hospital and Research Institute, Multan, Pakistan
**Corresponding author`s email address:* mahnoor808@gmail.com

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Abstract: *Meconium aspiration syndrome (MAS) is a significant cause of neonatal morbidity and mortality, particularly in resource-limited settings like Pakistan. Inhaled corticosteroids, such as budesonide, have shown promise in reducing pulmonary inflammation and improving respiratory outcomes. This study aimed to evaluate the efficacy of inhaled budesonide compared to normal saline in reducing respiratory distress, oxygen dependency, and hospital stay among neonates with MAS.* ***Methods:*** *A randomized controlled trial was conducted in the Department of Pediatric Medicine, Ibn-e-Siena Hospital, Multan, Pakistan, over six months from May 2024 to October 2024. Sixty neonates (≥34 weeks' gestational age) diagnosed with MAS were randomly assigned to two groups: Group A received inhaled budesonide (50 µg in 2.5 mL normal saline via nebulization every 12 hours), while Group B received normal saline nebulization as a control. The primary outcome was the mean time to normalization of Down's score. Secondary outcomes included the duration of oxygen therapy and total length of hospital stay. Data were analyzed using SPSS version 23, with $p < 0.05$ considered statistically significant.* ***Results:*** *The mean age of neonates was 10.4 ± 3.2 hours, and 60% were male. Baseline characteristics were comparable between both groups ($p > 0.05$). The mean time to normalization of Down's score was significantly shorter in the budesonide group (3.54 ± 1.41 days) compared to the saline group (5.73 ± 1.48 days) ($p < 0.001$). Similarly, the mean duration of oxygen therapy was markedly reduced in the budesonide group (65.9 ± 28.6 hours vs. 100.8 ± 29.1 hours, $p < 0.001$). Hospital stay was also shorter in the budesonide group (4.33 ± 2.95 days vs. 5.77 ± 3.10 days, $p = 0.02$). The results remained significant across stratified analyses for gestational age, gender, and birth weight.* ***Conclusion:*** *Inhaled budesonide significantly improves respiratory outcomes in neonates with meconium aspiration syndrome by reducing the duration of respiratory distress, oxygen dependency, and hospital stay. Incorporating inhaled budesonide into standard MAS management protocols could enhance neonatal recovery and reduce healthcare burden, particularly in low-resource settings like Pakistan.*

Keywords: Meconium aspiration syndrome, budesonide, neonatal respiratory distress, Down's score, Pakistan, randomized controlled trial

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Introduction

Meconium aspiration syndrome (MAS) remains a significant cause of morbidity and mortality among neonates, particularly in cases of meconium-stained amniotic fluid. The syndrome arises when a newborn inhales a mixture of meconium and amniotic fluid into the lungs, which can cause airway obstruction and trigger a cascade of inflammatory responses (1,2). Evidence from current literature indicates that MAS can lead to severe respiratory distress, affecting gas exchange and overall pulmonary functionality in affected neonates (3,4). Furthermore, the inflammation associated with meconium can compromise surfactant function, exacerbating the respiratory challenges these neonates face (5,6).

Recent studies have highlighted the critical role of corticosteroids, particularly inhaled budesonide, in the management of MAS. Budesonide is a glucocorticoid that, when delivered via inhalation, has shown promise in mitigating lung inflammation (7,3,8). The administration of budesonide in conjunction with surfactant therapy has been explored as a combined technique to enhance lung function in neonatal models of MAS. Studies suggest that the addition of budesonide not only reduces inflammation but also improves surfactant restoration and lung mechanics, indicating a potential synergistic effect that warrants further exploration as a therapeutic strategy in human neonates (9,10).

Clinical trials and observational studies have corroborated these findings, reporting significant reductions in the duration and severity of respiratory distress in neonates treated with inhaled budesonide compared to traditional management strategies (11,7,3). Specifically, one trial demonstrated that nebulized budesonide effectively reduced the oxygen requirement and the duration of hospitalization for affected neonates, emphasizing its potential as a pivotal treatment modality in the management of MAS (8,11,3). The effect of budesonide is believed to stem from both direct anti-inflammatory actions and its impact on airway reactivity and responsiveness, which are particularly beneficial in the inflamed and compromised lungs of neonates with MAS (3,6,9).

In Pakistan, with increasing rates of neonatal respiratory distress associated with meconium aspiration and the burden on neonatal intensive care units, the incorporation of inhaled budesonide in treatment protocols could significantly impact clinical outcomes. Economic considerations, along with available resources and current healthcare practices, make inhaled corticosteroids a feasible intervention that may reduce neonatal morbidity associated with MAS. The favorable outcomes reported in recent studies underscore the importance of integrating evidence-based practices into the management of neonatal conditions, including MAS. Thus, there is an imperative to investigate further local population responses to inhaled budesonide, incorporating demographic and epidemiological considerations into future research.

Methodology

This randomized controlled trial was conducted in the Department of Pediatric Medicine at Ibn-e-Siena Hospital, Multan, Pakistan, over 6 months from May 2024 to October 2024, following ethical approval from the institutional review board. The study aimed to compare the clinical outcomes of inhaled budesonide with normal saline in neonates diagnosed with meconium aspiration syndrome (MAS). The study population consisted of neonates admitted to the neonatal intensive care unit who

fulfilled the diagnostic criteria of MAS. A total of sixty neonates were enrolled after obtaining written informed consent from their parents or guardians. Eligible participants included both male and female neonates with a gestational age of 34 weeks or more, admitted with a Diagnosis of MAS based on clinical and radiological evidence. The diagnosis of MAS was confirmed in neonates delivered through meconium-stained amniotic fluid with retrieval of meconium from below the larynx on endotracheal suction, who developed respiratory distress within four hours of birth, persisting beyond twenty-four hours, with chest radiographs demonstrating infiltrations, hyperinflation, or atelectasis, and absence of any other cause of respiratory distress.

Neonates with clinical or laboratory evidence of sepsis, systemic illness, congenital anomalies, preterm birth before 34 weeks, intrauterine growth restriction (IUGR), or those whose parents declined consent were excluded. A non-probability consecutive sampling technique was used to enroll the study participants until the desired sample size was achieved. The sample size of sixty neonates (thirty in each group) was calculated using OpenEpi software, assuming a mean difference in time to normalization of Down's score between budesonide and normal saline groups (3.5 ± 1.5 days vs. 5.7 ± 1.5 days, respectively), with a power of 80% and a confidence level of 95%.

After enrollment, demographic and baseline clinical data were recorded using a pre-designed proforma. Variables included neonatal age in hours, gender, birth weight, gestational age, maternal age, mode of delivery, and baseline Down's score. The Downs' score, a validated clinical tool for evaluating respiratory distress, was used for continuous monitoring and clinical assessment. It consists of six parameters —respiratory rate, retractions, cyanosis, air entry, and grunting—each scored from 0 to 2, for a total possible score of 10. A score below four was considered indicative of normalization of respiratory status.

Participants were randomly assigned to one of two groups using a sealed opaque envelope method to ensure allocation concealment. Group A received inhaled budesonide therapy, whereas Group B received nebulized normal saline as a control. The budesonide group received a 50 µg dose diluted in 2.5 mL of normal saline via a jet nebulizer every 12 hours, beginning on the second day of life. It continued for up to 7 days or until clinical recovery, whichever occurred earlier. The control group received 0.15 mL/kg of 0.9% normal saline through nebulization following the same frequency and duration. All neonates received standard supportive care, including oxygen supplementation, maintenance of body temperature, and intravenous fluids at 60 mL/kg/day for term neonates and 80 mL/kg/day for preterm neonates, in accordance with neonatal care protocols.

Continuous clinical monitoring was performed by the attending neonatologist and trained nursing staff, who were blinded to group allocation. Vital signs, respiratory rate, work of breathing, and oxygen saturation were recorded at three-hour intervals using pulse oximetry. Down's scores were measured every six hours by an independent physician who remained unaware of the treatment assignment to minimize observer bias. The decision regarding initiation and discontinuation of oxygen therapy and patient discharge was made by a consultant neonatologist based on standardized clinical criteria.

The primary outcome measure was the mean time (in days) to normalization of the Down's score. Secondary outcomes included duration of oxygen therapy (in hours) and total length of hospital stay (in days). Data were analyzed using IBM SPSS version 23. Normality of quantitative data was tested using the Shapiro–Wilk test. Quantitative variables such as age, gestational age, maternal age, birth weight, Down's score, time to normalization of Down's score, duration of oxygen therapy, and length of hospital stay were expressed as mean ± standard deviation. Qualitative variables, including gender, gestational age group (late preterm or term), mode of delivery, and low birth weight status, were presented as frequencies and percentages.

Comparisons between the two study groups were performed using the independent samples t-test for continuous variables and the chi-square test for categorical variables. A p-value less than 0.05 was considered statistically significant. Stratification by gestational age, gender, mode of delivery, maternal age, and birth weight was performed to evaluate their potential influence on the primary outcomes. Post-stratification analyses were conducted using independent-samples t-tests to determine statistical significance within subgroups.

Results

A total of 60 neonates diagnosed with meconium aspiration syndrome were enrolled and randomized into two equal groups: Group A (Inhaled Budesonide) and Group B (Normal Saline). The mean age of neonates at presentation was 10.4 ± 3.2 hours, with 36 (60%) males and 24 (40%) females. The mean maternal age was 27.8 ± 4.3 years. The mean gestational age of the enrolled neonates was 37.9 ± 1.3 weeks, and the mean birth weight was 2.81 ± 0.42 kg. Low birth weight (<2.5 kg) was noted in 18 (30%) cases. Normal vaginal delivery (SVD) accounted for 39 (65%) cases, while 21 (35%) were delivered via caesarean section. There were no statistically significant differences between the two groups in baseline characteristics ($p > 0.05$ for all). (Table 1)

Table 1: Demographic and Baseline Characteristics of the Study Population (n = 60)

Variable	Total (n=60)	Group A (Budesonide) *(n=30)*	Group B (Normal Saline) *(n=30)*	p-value
Mean age (hours)	10.4 ± 3.2	10.1 ± 3.3	10.8 ± 3.1	0.52
Gender				
• Male	36 (60%)	18 (60%)	18 (60%)	1.00
• Female	24 (40%)	12 (40%)	12 (40%)	
Maternal age (years)	27.8 ± 4.3	27.4 ± 4.1	28.1 ± 4.4	0.61
Gestational age (weeks)	37.9 ± 1.3	38.0 ± 1.4	37.8 ± 1.2	0.68
Birth weight (kg)	2.81 ± 0.42	2.83 ± 0.39	2.79 ± 0.45	0.71
Low birth weight (<2.5 kg)	18 (30%)	8 (26.7%)	10 (33.3%)	0.57
Mode of delivery				
• SVD	39 (65%)	20 (66.7%)	19 (63.3%)	0.78
• C-section	21 (35%)	10 (33.3%)	11 (36.7%)	
No statistically significant difference between groups at baseline				

The mean time to normalization of Down's score was significantly shorter in the Budesonide group (3.54 ± 1.41 days) compared to the Normal Saline group (5.73 ± 1.48 days) ($p < 0.001$). Similarly, the duration of oxygen therapy was markedly reduced in the Budesonide group (65.9 ± 28.6 hours) compared to the control group (100.8 ± 29.1 hours) ($p < 0.001$). The mean duration of hospitalization was also significantly shorter among neonates receiving inhaled Budesonide

(4.33 ± 2.95 days) compared to those receiving saline (5.77 ± 3.10 days) (p = 0.02). (Table 2)

Table 2: Comparison of Clinical Outcomes Between the Two Study Groups

Outcome Variable	Group A (Budesonide) *(n=30)*	Group B (Normal Saline) *(n=30)*	Mean Difference (95% CI)	p-value
Time to normalization of Down's score (days)	3.54 ± 1.41	5.73 ± 1.48	–2.19 (–2.96, –1.42)	<0.001*
Duration of oxygen therapy (hours)	65.9 ± 28.6	100.8 ± 29.1	–34.9 (–49.0, –20.8)	<0.001*
Duration of hospital stay (days)	4.33 ± 2.95	5.77 ± 3.10	–1.44 (–2.73, –0.15)	0.02*
*Statistically significant at p < 0.05				

After stratifying by gestational age, gender, and birth weight, the beneficial effects of Budesonide on time to normalization of Down's score and duration of oxygen therapy remained statistically significant (p < 0.05 in all subgroups). However, no significant interactions were observed with mode of delivery or maternal age. (Table 3)

Table 3: Stratified Analysis of Time to Normalization of Down's Score

Variable	Category	Group A (Budesonide) *(Mean ± SD)*	Group B (Normal Saline) *(Mean ± SD)*	p-value
Gestational age	Term (≥37 weeks)	3.47 ± 1.30	5.64 ± 1.51	<0.001*
	Late preterm (34–36 weeks)	3.78 ± 1.49	5.89 ± 1.45	0.002*
Gender	Male	3.56 ± 1.32	5.65 ± 1.40	<0.001*
	Female	3.51 ± 1.50	5.86 ± 1.52	<0.001*
Low birth weight	Yes	3.75 ± 1.29	5.90 ± 1.40	0.001*
	No	3.49 ± 1.42	5.64 ± 1.47	<0.001*
*Statistically significant				

The mean time to normalization of Down's score and duration of oxygen therapy were significantly reduced with inhaled Budesonide. The hospital stay was also shorter in the intervention group, suggesting faster recovery and lower healthcare costs.

Discussion

The findings from our study demonstrate the beneficial effects of inhaled budesonide in neonates with meconium aspiration syndrome (MAS), particularly on respiratory outcomes and hospitalization length. Specifically, the mean time to normalization of the Down's score and the duration of oxygen therapy were significantly shorter in the budesonide group than in the normal saline group. Additionally, the mean hospitalization duration was shorter among neonates receiving inhaled budesonide. These results align well with the current literature, which endorses the efficacy of corticosteroids, including budesonide, in managing inflammatory conditions associated with MAS (12,13).

Our study population's demographics were comparable to those reported by Ahmed et al. (14), who also found that demographic variables such as sex, gestational age, and mode of delivery did not significantly correlate with MAS severity. With a mean birth weight of 2.81 kg, our results support findings from Bhandari et al. Bhandari et al. (15) et Jain et al. Jain et al. (16) that birth weight is a significant concern in the context of MAS, as it affects morbidity rates. Importantly, the lack of statistically significant differences between groups in baseline characteristics further substantiates that the observed clinical outcomes are attributable to treatment effects rather than confounding demographic factors.

The reduction in time to normalization of Down's score from 5.73 days in the saline group to 3.54 days in the budesonide group corroborates findings reported by Phattraprayoon et al. (12), who conducted a systematic review revealing that steroid treatments notably reduced the duration of respiratory symptoms in neonates with MAS. Similarly, our results indicate a significant reduction in the duration of oxygen therapy, consistent with findings from Elfarargy et al. (17), who demonstrated that inhaled budesonide effectively shortened oxygen dependency in neonates with respiratory distress.

The mean hospitalization duration in the budesonide group was 4.33 days, significantly lower than that in the saline group (5.77 days; p = 0.02). This result echoes the work of Hapsari and Pratidina (18), who highlighted that a more rapid recovery can lead to lower healthcare costs and reduced strain on neonatal units. The findings reinforce the notion that interventions that hasten recovery may also benefit healthcare economics, particularly in resource-constrained settings.

The stratified analysis confirms the robustness of our results across different demographic variables, with the beneficial effects of budesonide being statistically significant regardless of gestational age, gender, or low birth weight; however, prior studies, such as those by Agarwal et al. Tantu et al. (19) and Gupta et al. (20) indicated variations in responses based on these demographics. The homogeneity of our findings across subgroups suggests that budesonide may offer a universally applicable treatment strategy for MAS in neonates.

Further, our findings align with the literature, which portrays inhaled budesonide as a viable adjunct therapy for MAS management. As indicated by Sayed et al. (13) and corroborated by Liu et al. (21), inhaled corticosteroids can offer considerable benefits in addressing the pulmonary inflammation that often characterizes MAS.

In conclusion, the current study provides compelling evidence that inhaled budesonide can significantly improve clinical outcomes in neonates with MAS, reducing the duration of respiratory distress and hospital stay.

In Pakistan, the incidence and consequences of meconium aspiration syndrome remain a critical public health concern, particularly in light of high rates of neonatal respiratory distress as discussed by Tanveer et al. (22). The implementation of inhaled budesonide in clinical practice could not only enhance patient outcomes but also alleviate pressure on healthcare resources, making it a vital consideration for neonatal care strategies in the country.

Conclusion

Inhaled budesonide proved an effective adjunct therapy in neonates with meconium aspiration syndrome, leading to earlier improvement in respiratory function and shorter hospitalization time. Its ease of administration and favorable safety profile make it a practical addition to existing treatment protocols in Pakistani neonatal care units. Integration of budesonide therapy could not only improve clinical outcomes but also

optimize resource utilization in settings with limited intensive care capacity.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-24)
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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

MN (PGR Paediatric Medicine)
Manuscript drafting, Study Design,
SM (Professor, Head of Department)
Review of Literature, Data entry, Data analysis, and drafting articles.
SW (Assistant professor)
Conception of Study, Development of Research Methodology Design,
AJ (Associate Professor)
Study Design, manuscript review, critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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