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ROLE OF STEROIDS IN MECONIUM ASPIRATION SYNDROME

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ABSTRACT

Background: Meconium aspiration syndrome (MAS) is a significant contributor to neonatal respiratory morbidity especially in low-resource countries. Corticosteroids can potentially play a therapeutic role since inflammation plays a role in its pathophysiology.

Objective: To compare the efficacy of intravenous methylprednisolone and nebulized beclomethasone in improving clinical outcomes in neonates with moderate to severe MAS.

Methods: This was a randomized and blinded controlled trial which was conducted at the Department of Neonatology, Children Hospital Lahore during March 2022 to October 2022. A group of one hundred and ten (>35 weeks gestation) neonates with moderate or severe MAS, were randomly randomized to three (control (n=36), intravenous methylprednisolone n=37), and nebulized beclomethasone (n=37). The primary results were the positively affecting respiratory distress (Downes score and respiratory rate), the duration of respiratory distress, and oxygen demand. The secondary outcomes were duration of stay in the hospital, mechanical ventilation and mortality. Statistical analysis was done with SPSS v27, ANOVA and post hoc; $p<0.05$ was taken to be significant.

Results: The respiratory distress was significantly improved in both steroid groups, as compared to the controls, and the lower Downes scores ($p<0.003$) and respiratory rates ($p<0.012$). Duration of respiratory distress (p<|human|>Oxygen therapy (p<|human|>Hospital stay (p<|human|>Mechanical ventilation (p<|human|>Mechanical ventilation (p<|human|>Significant decreases were seen in duration of respiratory distress (p<|human|>Oxygen therapy (p<|human|>Hospital stay (p<|human IV methylprednisolone proved to be more effective than nebulized beclomethasone especially in alleviating respiratory distress ($p=0.0012$). There was no significant difference in mortality among groups ($p=0.6$).

Conclusion: Corticosteroids are useful in MAS, but do not influence mortality. IV methylprednisolone seems to be more effective than the nebulized beclomethasone.

INTRODUCTION

The passing of meconium in the labour process complicates an average of 7–20% of all pregnancies around the world, with an estimated 30% of babies being born with the consequences of meconium passage, the so-called meconium-stained amniotic fluid.[1–3] [4]

MAS has a complex pathophysiology. Hypoxemia, ventilation perfusion mismatch, and regional atelectasis cause intrapulmonary shunting and PPHN that causes extrapulmonary shunting.[8] More so, meconium aspiration syndrome is a neutrophil chemoattractant.[10] It also causes increased production of pro-inflammatory cytokines like tumour necrosis factor and interleukins (IL-1, IL-6, IL-8) that further aggravate the situation, leading to vascular leak, hemorrhagic pulmonary edema, and toxic pneumonitis.[1]

Corticosteroids appear to have the potential to be helpful, keeping in mind inflammation as one of the major contributors to the pathophysiology of MAS. Several steroid preparations have been tried to dampen the inflammatory response, and it is known that steroids can prevent the production of pro-inflammatory cytokines in vitro.[9],[10]

Dehan M et al.[11] found methylprednisolone effective, with reduced side effects compared to dexamethasone. On the other hand, Garg et al.[12] and Patil et al.[13] have shown that steroids are a beneficial and preferable mode of treatment in MAS as compared to intravenous and nebulised steroids with control.
We were able to locate very little literature that addressed the use of inhaled beclomethasone in MAS, but it has been extensively used in neonates and has proven to be a safe and effective substitute for injectable steroids.[21],[22] We desired to quantify and contrast the impacts of systemic and nebulised corticosteroids on the clinical course and outcome of MAS.

MATERIAL AND METHODS

This Double blind, Randomised controlled trial was started at the Department of Neonatology, The Children's Hospital & the Institute of Child Health, Lahore from March 2022 to October 2022. The sample size was calculated using G Power software and to counter the impact of the effect of attrition10% sample was added to the cumulated sample. The total number of samples was 110; Control (Group A): 36, IV steroids (Group B): 37, Nebulised steroids (Group C): 37.
The inclusion criteria were; Gestational age more than 35 weeks, moderate to severe MAS that manifested between 24 hours of life. While neonates having sepsis, HIE stage III, Congenital malformation, history of ventilatory support at other hospitals, suspected Inherited metabolic defect, Shock and Intraventricular Hemorrhage were excluded.
The parents/guardians were informed and offered an opportunity to take part in the study by informing them about the study, giving a comprehensive history and a thorough examination of the neonates who met the criteria. Computer generated method (double blind) was used to randomise the sample size of the patients to three groups. Group A (Control) was pre decided to be given supportive treatment (fluids, oxygen) and surfactant where indicated, according to departmental protocols along with placebo (Intravenous NS with nebulised NS) 12 hourly for 3 days starting from 48 hours of life in cases of moderate and severe MAS.Group B was treated with 0.25 mg/kg/dose of Intravenous Methylprednisolone combined with nebulized NS 12 times every hour on the 3 days of life as an addition to supportive treatment program of our department. Group C: Supportive care (fluids, oxygen) and surfactant were given on an as needed basis according to departmental guidelines and nebulised Beclomethasone 400mcg/dose and Intravenous NS 12hourly 3days beginning 48 hours of life. The most significant outcome measure was to ascertain the impact of steroids on respiratory distress (Downes score and slowed respiratory rate), length of respiratory distress (reduced mean number of days in all three groups) and oxygen demand. The secondary outcome variable was to compare the effect of steroids on hospital stay as compared to controls and mortality.
Any short term adverse effects were reported. The SPSS version 27.0 was used to analyse data. There were 3 level of analysis that were identified; descriptive, inferential and effect size. Frequency and percentages were used to measure demographic characteristics. The clinical parameters i.e., age, weight, days of oxygen therapy, days of feeding were presented using mean and standard deviation. The data was tested to determine the normality in order to determine whether to use parametric at the inferential level or not. The determination of comparison of the three groups and determination of inter group statistical significance was done using ANOVA and post hoc test respectively. The qualitative findings such as complications were analysed with sorting similar and dissimilar findings and expressed in the form of frequency if observed during the course of study. P value that is below 0.05 was considered to be significant.

RESULTS

Total 110 patients were enrolled in three groups; Group A (n = 36); Group B (n = 37) and Group C (n = 37). The profile of patients of the three groups was similar since all of them were randomised by using computer generated system and they were also blinded. Group A, B and C had an average age(days) at presentation of 1:+.5, 1:+.6, 1.2:+.4 respectively. The average gestational age of control and intervention groups is as in table 1.
Steroids failed to show any effect on the overall in-hospital mortality in moderate to severe MAS in comparison to controls (p-value=0.6).
There was marked improvement in Downes Score in intervention group B and C as compared to controls as mentioned in Table. Post Hoc test indicated that IV steroid(group B) had more significance in alleviating respiratory distress as compared to group C.
Both IV methylprednisolone and inhaled beclomethasone were found to decrease respiratory distress(p-value=0.012), duration of respiratory distress(p-value=0.002), reduction in duration of oxygen therapy(p-value=0.0.042), shortening of hospital stay(p-value=0.04), and duration of mechanical ventilation (p-value=0.001). Group B, in general, was significantly better than Group C in all outcome variables which had improved. This was more evident in alleviating respiratory distress (p-value=0.0012).

Table 1: Study Groups: Characteristics and Clinical Outcomes at Baseline.

Variable	Group A (Control) (n=36)	Group B (IV Methylprednisolone) (n=37)	Group C (Nebulized Budesonide) (n=37)

Sex (Male:Female)	17:19	20:17	17:20
Gestational Age (weeks)	38.8 ± 2.92	38.91 ± 2.56	39.3 ± 2.60
Age at Presentation (days)	1.0 ± 0.5	1.0 ± 0.6	1.1 ± 0.4

Table 2: Outcome Variables

Variable	Group A (Control)	Group B (IV Steroid)	Group C (Neb Steroid)	p-value	Post Hoc (B vs C)
Downes Score	2.86 ± 2.01	1.55 ± 1.46	1.45 ± 1.42	<0.003	0.003
Respiratory Rate at Day 6 (breaths/min)	78.56 ± 4.56	65.34 ± 6.24	64.11 ± 7.12	<0.012	0.0012
Duration of Respiratory Distress (days)	5.7 ± 2.2	3.56 ± 1.8*	2.52 ± 1.6*	<0.002	0.035
Duration of Oxygen Therapy (days)	5.7 ± 2.2	3.45 ± 1.7*	2.97 ± 1.5*	<0.013	0.042
Hospital Stay (days)	12.0 ± 2.44	10.44 ± 2.55	10.78 ± 1.45	<0.04	0.031
Mechanical Ventilation (days)	8.0 ± 3.2	6.10 ± 1.32	6.45 ± 1.78	<0.001	0.062
Mortality (n)	3	2	3	0.60	—

DISCUSSION

Our study concluded that overall steroids were effective in improving primary and secondary outcomes in MAS as compared to control group; they did not alter the outcome of in-hospital mortality in both intervention groups as compared to controls.[17]

In our study involving 110 patients, (IV) methylprednisolone and nebulised beclomethasone improved respiratory distress that was measured by both; improved respiratory rate and Downes score in intervention group B and C (p value 0.003). Similar results were seen in a study by Basu et al.[16] It is pertinent to mention here that our study differed in both dosing and timing of IV methylprednisolone and type of nebulised steroid (beclomethasone vs budesonide), yet we had comparable results. Steroids were started 48 hours after birth and in a lesser dose that also resulted in marked improvement in respiratory distress in both intervention groups (B and C) as compared to controls.

Significant effect was also seen in reduction of oxygen need and shortening of hospital stay when comparing IV methylprednisolone to nebulised steroids in our study (MD, -3.45 days vs MD, -2.97 days) and (MD, -4.5 days vs MD, -2.5 days). These results were somehow comparable to a systematic review and meta-analysis (MD, -3.30 days vs MD, -2.40 days) and (MD, -7.23 days vs MD, -4.47 days).[17] However, these results differed from a study that found no difference in reduction of hospital stay between controls and intervention groups.[18]

While evaluating our secondary outcome measures, it was revealed that there was no effect on mortality in MAS in all three groups ($p < 0.6$). This was also reported in another study which concluded the beneficial effect of steroids on respiratory distress but no decrease in mortality.[17]

Another systematic review and meta-analysis of randomized controlled trials (RCTs) found budesonide nebulization resulting in significant early improvement in respiratory distress (p value < 0.01) and early normalization of Downes score with lesser oxygen requirement ($p < 0.001$), but had no impact on final outcome.[19]

Positive outcome of steroids on decrease in mechanical ventilation (reduction of mean days) was determined in different randomized controlled trials.[20],[21] Our results were also aligned with decrease in mean days on ventilation in MAS (p value 0.001). This was in contrast to another study which revealed no significant difference.[22]

CONCLUSION

Steroids do not increase mortality but in some way, they are effective in the management of meconium aspiration syndrome. Use of steroids must take into account patient centred approach in choosing the type and route of administration but this needs bigger studies to warrant their efficiency and optimal use.

CONFLICT OF INTEREST: All the authors do not have any conflict of interest in this study.

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DISCLAIMER: This research has neither been submitted nor reported in any conference or journal.
The study has the following strengths.

Our research was a randomised controlled trial which was narrowed down to a comparative study of efficacy of steroid in improving MAS not unusual in resource limited settings.

STUDY Limitations.

A limitation of this study was the fact that there could be a confounding variable of the severity of meconium aspiration syndrome (MAS). Also, evaluation of long-term effects of steroids such as neurodevelopmental was not easy due to relatively short follow-up period which again complicated the process of recording of steroids safety and safe effective dose.

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