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# Effect of nebulized budesonide in improving the clinical outcome of neonates with meconium aspiration syndrome

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**Abstract:**

**Aim and Objective:** To study the effect of nebulized steroid in improving the clinical outcome in terms of morbidity and mortality in neonates with meconium aspiration syndrome.

**Design:** Prospective open labeled randomized controlled trial.

**Setting:** Tertiary care teaching hospital.

**Patients:** Full term babies with diagnosis of meconium aspiration syndrome(MAS) admitted in the NICU of Cheluvamba Hospital attached to Mysore Medical College and Research Institute were included in the study.

**Intervention:** Administration of nebulized budesonide in a dose of 50µg in 2.5ml normal saline through jet nebulizer every 12hourly from second day of life till 7days or clinical recovery whichever is earlier.

**Results:** A Total of 60 patients with diagnosis of MAS were admitted to the NICU during the period of August - October 2013, out of them 20 were excluded, so a total of 40 patients were included in the study, 20 in control group (Group A), 20 in budesonide group (Group B). The baseline clinical profile of both the groups were similar. Duration of respiratory distress in days (2.63 vs 5.24 p=0.0493), duration of oxygen dependency (2.37 vs 4.94 p=0.0406), duration of hospital stay (7.58 vs 10.47 p=0.0430), time taken for achievement of full feeds (3.79 vs 8.76 p=0.0002) and the need for mechanical ventilation (0 vs 0.2 p=0.0356) were statistically less in budesonide treated group as compared to the controls. Incidence of sepsis is similar in both the groups. Complications were similar in both the groups and no specific adverse effects were noted in the steroid treated group. Four patients died during the hospital stay, three in the control group and one in the case group. Out of them two patients died due to pneumothorax and both of them belong to the control group, other two patients died due to sepsis with disseminated intravascular coagulation(DIC), representing one each from control and case group.

**Conclusion:** Nebulized budesonide improves the clinical outcome in terms of morbidity and is relatively safe, however long term follow-up is needed to recommend inhalation route of steroids as safe and effective.

**Keywords:** Budesonide, Meconium aspiration syndrome, Steroid

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## Introduction

Meconium aspiration syndrome (MAS) is one of the most common cause of respiratory distress. The overall incidence of meconium stained amniotic fluid (MSAF) is 12% of live births and MAS occurs in approximately 35% of them or 4% of all live births [1].

Treatment is mainly supportive like oxygen supplementation and assisted ventilation along with fluids and electrolytes, preventive strategies like oro-pharyngeal and endo-tracheal suctioning are done but still many babies develop MAS [2].

Meconium aspiration leads to activation of macrophages producing intense inflammatory response and infiltration of polymorphonuclear lymphocytes into the lungs. There is associated increase in the vascular permeability causing protein exudation into the alveolar spaces and thereby causing inactivation of the surfactant [3]. since inflammation plays an important role in the pathophysiology of MAS, anti-inflammatory drugs like corticosteroids may be beneficial in treating neonates with MAS. At present there is insufficient evidence to assess the benefits and harms associated with steroids in MAS [4].

In view of paucity of literature in role of nebulized steroids in determining the outcome of neonates with MAS, there is a need to study its role in improving the clinical outcome of neonates with MAS. In the present study we have evaluated the efficacy of nebulized budesonide in improving the clinical outcome of neonates with MAS.

## MATERIALS AND METHODS

### Study design

A randomized controlled trial conducted in the neonatal intensive care unit (NICU), Department of Pediatrics, Mysore Medical College and Research Institute, over a period of 3months (August-October 2013). The study was approved by the hospital ethical committee. Informed written consent was obtained from the parents.

Full term babies with the diagnosis of MAS as per the criteria given by Gerand et al. [9] were

included in the study. Diagnosis was done based on the following criteria.

- a. Delivery through MSAF
- b. Retrieval of meconium from below the larynx on endotracheal suction.
- c. Development of respiratory distress within 4 hour after birth and persistence beyond 24 hours.
- d. Chest xray showing infiltrations, hyperinflation and atelectasis
- e. Absence of any other cause of respiratory distress.

Exclusion criteria were clinical or investigation based evidence of sepsis, the presence of any systemic illness, the presence of any gross congenital malformations, preterm and IUGR babies, parents denied consent for the trial.

Sample size calculation was done based on the formula  $n = Z^2 (pq) / d^2$ , where  $z = 1.96$ ,  $p$  is the Incidence of MAS which was taken as 0.004,  $q = (1-p)$ ,  $d$  is the confidence interval taken as 0.05, applying  $\alpha$  of 0.05 and power  $(1-\beta)$  of 80% as per WHO manual of sample size determination [5]. We have taken a sample size of 20 controls and 20 cases. Randomization was done by computer generated random numbers and patients were divided into two groups, Group A – controls and Group B – cases. controls received normal saline nebulization and cases received Budesonide nebulization.

Neonates included in the study were assessed clinically. Sepsis screening and chest x-ray was done at the time of admission.

Group B received nebulized budesonide (Budecort, Cipla) in a dose of 50 $\mu$ g in 2.5ml normal saline through jet nebulizer every 12hourly from second day of life till 7 days or clinical recovery whichever was earlier. Group A received normal saline nebulization.

Neonates in both the groups received supportive management according to the standard protocols of our nursery, clinical parameters assessed were daily vitals, clinical score of respiratory distress [8] and development of any complications (hyperglycemia, hypoglycemia, hypotension, hypocalcemia and hyperbilirubinemia).

Blood culture and repeat chest X-ray was done on Day 7 or at the time of clinical recovery whichever was earlier. Patients were called for follow-up once in two weeks for 3 months.

Outcome variables:

- 1.Duration of respiratory distress
- 2.Duration of oxygen dependency
- 3.Duration of hospital stay
- 4.Time taken for full feeds
- 5.Need for mechanical ventilation

Statistical analysis: Data were analysed by SPSS software version 20.0. Statistical significance was calculated by student's t-test and chi-square test. The p-value <0.05 is taken as statistically significant.

## RESULTS

A total of 60 patients with diagnosis of MAS were admitted to the NICU during the period of August-October 2013. After drop-out 20 newborns, total of 40 patients were included in the study, 20 in control group (Group A), 20 in budesonide group (Group B). The baseline clinical profile of both the groups were similar (Table 1).

Progress during the hospital stay has been summarized (Table 2). Duration of respiratory distress in days (2.63 vs 5.24 days, p=0.0493),

duration of oxygen dependency (2.37 vs 4.94 days, p=0.0406), duration of hospital stay (7.58 vs 10.47 days, p=0.0430), time taken for achievement of full feeds (3.79 vs 8.76 p=0.0002) and the need for mechanical ventilation (0 vs 0.2 p=0.0356) were statistically lower in budesonide treated group when compared to controls.

Incidence of sepsis is similar in both groups. A total of eight patients developed culture proven sepsis during the hospital stay. Complications were similar in both the groups and no specific adverse effects were noted in the steroid treated group. Four patients died during the hospital stay, three in the control group and one in the case group. Out of them two patients died due to pneumothorax and both of them belong to the control group, other two patients died due to sepsis with disseminated intravascular coagulation (DIC), representing one each from control and case group. Four patients were ventilated, all four belong to the control group and none from the case group. None of them developed primary pulmonary hypertension and nobody received pulmonary vasodilator. Three patients in the control group and two patients in the case group developed hypotension and required inotropic support.

**Table1. Baseline clinical profiles of study groups.**

	Control Group A (n=20)	Budesonide Group B (n=20)
<b>Mode of delivery</b>		
Normal vaginal delivery (%)	8(40)	7(35)
Caesarean section (%)	12(60)	13(65)
<b>Birth weight (gram; Mean±SD)</b>	2.815(0.195)	2.820(0.167)
<b>Male /Female</b>	13/7	15/5
<b>Apgar score at 5 minutess (Mean±SD)</b>	6.15(0.88)	5.95(0.76)
<b>RDS Score at initiation of treatment</b>	3.95(0.69)	3.80(0.77)

RDS-Respiratory distress syndrome, SD-standard deviation

**Table 2. Clinical outcomes of study group.**

	<b>Control Group A (n=17)</b>	<b>Budesonide Group B (n=19=)</b>	<b>p</b>
<b>Duration of Respiratory distress (days)</b>	5.24±5.48	2.63±0.96	<b>0.0493</b>
<b>Duration of oxygen dependency (days)</b>	4.94±5.24	2.37±0.60	<b>0.0406</b>
<b>Duration of Hospital stay(days)</b>	10.47±5.21	7.58±2.81	<b>0.0430</b>
<b>Time taken for full feeds (days)</b>	8.76±4.97	3.79±1.62	<b>0.0002</b>
<b>Need for mechanical ventilation(days)</b>	0.20±0.41	0.00±0.00	<b>0.0356</b>

Values expressed as mean ± standard deviation, \*P value is considered to be statistically significant(<0.05).

**Table 3. Complications observed during hospital stay among study patients.**

	<b>Control Group A (n=17)</b>	<b>Budesonide Group B (n=19=)</b>	<b>p</b>
<b>Meningitis</b>	1(0.05)	1(0.05)	1.0000
<b>Sepsis without meningitis</b>	3(0.15)	3(0.15)	1.0000
<b>Hypotension</b>	3(0.15)	2(0.10)	0.6429
<b>Pneumothorax</b>	2(0.10)	0(0.00)	0.1544
<b>Seizures</b>	2(0.10)	1(0.05)	0.5602
<b>Hyperglycemia</b>	1(0.05)	1(0.05)	1.0000
<b>Hypoglycemia</b>	3(0.15)	3(0.15)	1.0000
<b>Hypocalcemia</b>	0(0.00)	0(0.00)	0.0000
<b>Hyperbilirubinemia</b>	2(0.10)	2(0.10)	1.0000
<b>Mortality</b>	3(0.15)	1(0.05)	0.3040

## DISCUSSION

In the present study, the diagnosis of MAS was made as per the criteria given by Gerand et al. [9]. Steroids were used for the treatment of MAS way back in 1977 by Frantz et al. [10] in animal model, they showed promising results of clinical improvement but mortality was high. Yeh et al. [7] used hydrocortisone and found that it was ineffective as it prolongs the duration of stay,

oxygen requirement and respiratory distress. Dexamethasone was used by many [11] and all of them showed clinical improvement. Prednisolone was used in animal model by Kirimi et al. [12]. They showed reduced physiological and histological changes. Studies with budesonide in neonates with MAS are less, Tripathi et al. [6] showed both systemic methylprednisolone and nebulized budesonide

reduced the duration of oxygen dependency and duration of stay.

In the present study we have used nebulized budesonide starting after 24 hours of life till clinical recovery or 7 days, the rationale behind starting steroids after 24 hours was to exclude the cases in whom the respiratory distress got settled by 24 hours and were considered to be due to transient tachypnea of newborn. Rationale behind choosing budesonide was it has high topical activity, less systemic side effects and more potent than dexamethasone [13].

In the present study the clinical profile of both the groups were comparable, A statistically significant difference was found between the two groups, lesser duration of oxygen dependency and lesser duration of stay was observed in the steroid treated group as compared to controls, the duration of respiratory distress was significantly reduced by nebulized budesonide, neonates started taking full enteral feeds much earlier in budesonide treated group and mechanical ventilation was not required in budesonide group. Mortality was seen more in controls rather than case group although statistically not significant. Regarding adverse effects, there was no statistical difference found between the two groups in terms of short term complications like sepsis, hyperglycemia, hypoglycemia, hyperbilirubinemia and hypocalcemia. The need for mechanical ventilation and mortality were not studied in any of the previous studies.

Limitations of our study were, first the study was not blinded but neither the caregivers nor the data collectors were biased with the study, with the analysis being done by a person who is not part of the study. Secondly only short term complications were studied here and long term follow-up is needed for complications such as neurodevelopmental outcome, thirdly the sample size was less and larger studies are necessary to recommend steroid nebulization in the routine management of MAS.

In conclusion, nebulized budesonide improves the clinical outcome in terms of morbidity and is relatively safe, however long term follow-up is

needed to recommend inhalation route of steroids as safe and effective.

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