Int J Biol Med Res.2015;6(2):4942-4945

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

Effect Of Nebulized Budesonide In Improving The Clinical Outcome Of Neonates With Meconium Aspiration Syndrome.

Suresh R,

Post graduate student, Dept of pediatrics,Mysore Medical College & Research Institute, Irwin Road, Mysore – 570001.

ARTICLE INFO

Keywords:
Budesonide
Meconium aspiration syndrome
Steroid

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 clinical 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(Budecort,Cipla) 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 40 patients with clinical diagnosis of MAS admitted to the NICU during the period of august - october 2013, 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 short term respiratory outcome and is relatively safe, however long term follow-up is needed to recommend inhalation route of steroids as safe and effective.

Introduction:

Meconium aspiration syndrome(MAS) is defined as respiratory distress in an newborn associated with meconium stained amniotic fluid, where the symptoms otherwise cannot be explained. The incidence of meconium stained amniotic fluid is 12% of live births and MAS occurs in approximately 35% of them or 4% of all live births inspite of preventive strategies like oro-pharyngeal and endo-tracheal suctioning[1].

Treatment is mainly supportive like oxygen supplementation and assisted ventilation along with fluids, electrolytes and management of complications e.g. Air Leak Syndromes and Persistent Pulmonary Hypertension" [2].

* Corresponding Author : **Suresh R,**
Post graduate student, Dept of pediatrics,
Mysore Medical College & Research Institute,
Irwin Road,
Mysore – 570001.
Email – surmbbs@gmail.com

Meconium is a source of pro-inflammatory cytokines, recruits macrophages and also it potentiates the chemotactic activity of neutrophils[3]. This leads to severe inflammatory reaction in the lung and proteolytic enzymes which are released from the neutrophilic granules may destruct the membranes and surfactant proteins and increase endothelial permeability [4]. since inflammation plays a key role in the pathophysiology of MAS, anti-inflammatory drugs like corticosteroids may improve the clinical status and survival of newborns with MAS. Early intratracheal instillation of budesonide can significantly improve the pulmonary outcome without causing long-term adverse effects[5]. At present there is insufficient evidence to assess the benefits and harms associated with steroids in MAS[6].

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:

A randomized controlled trial conducted in the neonatal intensive care unit(NICU), Department of pediatrics, Mysore medical college and research institute, mysore over a period of 6months (August 2013-January 2014). The study was approved by the hospital ethical committee. Informed written consent was obtained from the parents. Inclusion criteria were full term babies with clinical diagnosis of MAS as per the criteria given by Gerand et al[7] admitted in the NICU of cheluvamba hospital attached to Mysore medical college and research institute. Exclusion criteria were clinical or investigation based evidence of sepsis, presence of any systemic illness, presence of any gross congenital malformations, Preterm, IUGR babies and parents denied consent for the trial. Sample size calculation was done based on the formula $n=Z2\ (pq)/d2$, applying α of 0.05 and power (1-β) of 80% [8]. Here a sample size of 20 controls and 20 cases were taken. Randomization was done by computer generated random numbers and patients were divided into 2 groups, Group A as controls and Group B as 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 were done at the time of admission.

Group B - Received Nebulized budesonide(Budecort,cipla) 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 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 and development of any complications (hyperglycemia, hypoglycemia, hypotension, hypocalcemia and hyperbilirubinemia). Blood culture and repeat chest xray was done on day7 or at the time of clinical recovery whichever was earlier. Patients were called for follow-up once in two weeks for 3months. The following outcome variables were evaluated,

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

6.Short term complications on follow up

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. 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(Table 1). Progress during the hospital stay has been summarized(Table 2). 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 when compared to controls(Table 3).

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(Table 4). 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 during hospital stay and nobody received pulmonary vasodilator. Three patients in the control group and two patients in the case group developed hypotension and required inotropic support. During followup, one patient in both the groups developed primary pulmonary hypertension

TABLE 1 – Baseline clinical profile

Parameters	Control Group A;n=20	Budesonide Group B;n=20	p-value
Mode of delivery NVD(%) Caesarean(%)	8(40) 12(60)	7(35) 13(65)	0.6392
Birth weight(Mean±SD)	2.815(0.195)	2.820(0.167)	0.9311
Male /Female	13/7	15/5	0.3484
Apgar score at 5mins(Mean±SD)	6.15(0.88)	5.95(0.76)	0.4465 0.5204
RDS Score at initiation of treatment	3.95(0.69)	3.80(0.77)	

NVD - normal vaginal delivery, RDS-Respiratory distress, SD-Standard deviation

TABLE 2 - Clinical outcome

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

SD - Standard deviation, *P value is considered to be statistically significant(<0.05).

TABLE 3 - Complications during hospital stay

Parameters	Control Group A;n=20	Budesonide Group B;n=20	t-test p value
Meningitis	1(0.05)	1(0.05)	1.0000
Sepsis without meningitis	3(0.15)	3(0.15)	1.0000
Hypotension	3(0.15)	2(0.10)	0.6429
Pneumothorax	2(0.10)	0(0.00)	0.1544
Seizures	2(0.10)	1(0.05)	0.5602
Hyperglycemia	1(0.05)	1(0.05)	1.0000
Hypoglycemia	3(0.15)	3(0.15)	1.0000
Hypocalcemia	0(0.00)	0(0.00)	0.0000
Hyperbilirubinemia	2(0.10)	2(0.10)	1.0000
Mortality	3(0.15)	1(0.05)	0.3040

TABLE 4 - Comparison with other studies

Parameters	Basu s et al Group A;n=17	Tripathi s et al Group A;n=17	Present study Group B;n=19
Duration of Respiratory distress (days) (Mean±SD)	4.06±1.52	4.59±2.26	2.63±0.96
Duration of oxygen dependency (days) (Mean±SD)	4.06±1.52	4.59±2.26	2.37±0.60
Duration of Hospital stay (days) (Mean±SD)	12.18±6.22	10.63±1.56	7.58±2.81
Time taken for full feeds (days) (Mean±SD)	-	6.41±0.87	3.79±1.62
Need for mechanical ventilation(days) (Mean±SD)	-	-	0

SD - Standard deviation, *P value is considered to be statistically significant(<0.05)

DISCUSSION:

Steroids were used for the treatment of MAS since 1977 by frantz et.al.[9], they showed promising results of clinical improvement but mortality was high, Hydrocortisone was used by Yeh et al [10] and he found that it was ineffective as it prolongs the duration of stay, oxygen requirement and respiratory distress. Dexamethasone was used by many researchers[11] and all of them showed clinical improvement. Prednisolone was used in animal model by kirimi et al. [12] and he showed reduced physiological and histological changes. Studies with Budesonide in neonates with MAS are less, Tripathi et al[13] 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 24hrs of life till clinical recovery or 7days, the rationale behind starting steroids after 24hrs was to exclude the cases in whom the respiratory distress got settled by 24hrs 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[14].

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 ventillation 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. Similar findings were reported by Basu S et al[15] and Tripathi s et al as shown in Table 4. 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.

CONCLUSION:

Nebulized budesonide improves the short term respiratory outcome and is relatively safe, however long term follow-up is needed to recommend inhalation route of steroids as safe and effective.

References

1. Mhairi G.Macdonald, Martha D.Mullet, Mary M.K.Seshia. Avery's Neonatology 2005;6:562-565.

2. Jonathan M. Klein. Care of the Infant with the Meconium Aspiration Syndrome, Iowa Neonatology Handbook. The University of Iowa. 2006;1:143-144.

3. Craig S, Lopez A, Hoskin D, Markham F. Meconium inhibits phagocytosis and stimulates respiratory burst in alveolar macrophages. Pediatr Res 2005;57: 813-8.

4. Mokry J, Mokra D, Antosova M, Bulikova J, Calkovska A, Nosalova G. Dexamethasone alleviates meconium-induced airway hyperresponsiveness and lung inflammation in rabbits. Pediatr Pulmonol 2006;41:55-60.

5. Kuo HT1, Lin HC, Tsai CH, Chouc IC, Yeh TF. A follow-up study of preterm infants given budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants. J Pediatr. 2010 Apr;156(4):537-41.

6. Ward M, Sinn J. Steroid therapy for meconium aspiration syndrome in newborn infants. cochrane database syst Rev 2003;4:CD003485.

7. Gerand M, Cleary DO, Wistell TE. Meconium stained amniotic fluid and the meconium aspiration syndrome; an update. pediatr clin N Amer 1998;45:511-29.

8. Lwanga SK, Lemeshow S. Sample size determination in health studies; A Practical Manual. WHO;Geneva,1991.

9. Frantz ID, Wang NS, Thach BT. Experimental meconium aspiration; Effect of glucocorticoid treatment. J pediatr 1975;86:438-41.

10. T.F. Yeh, G. Srinivasan, V. Harris, R.S. Pildes. Hydrocortisone therapy in meconium aspiration syndrome; a controlled study. J pediatr 1977;90:140-3.

11. Andrew M, Davey AM. Randomized controlled trial of early dexamethasone therapy in the treatment of meconium aspiration syndrome. Pediatr Res 1995;37:329-35.

12. Kirimi E, Tuncer O, Kösem M, Ceylan E, Tas A, Tasal I. et al. The effects of prednisolone and serum malondialdehyde levels in puppies with experimentally induced meconium aspiration syndrome. J Int Med Res.2003;31:113-22.

13. Sandeep Tripathi, Saili A. The Effect of steroids on the clinical course and outcome of neonates with Meconium aspiration syndrome. J Trop Pediatr. 2007 Feb;53(1):8-12.\.

14. Halliday HL, Patterson CC, Halahakoon CW. A Multicenter randomized open study of early corticosteroid treatment in preterm infants with respiratory illness comparison of early and late treatment and of dexamethasone and inhaled budesonide. pediatrics.2001;107:232-40.

15. Basu S, Kumar A, Bhatia BD, Satya K, Singh TB. Role of steroids on the clinical course and outcome of meconium aspiration syndrome-a randomized controlled trial. J Trop Pediatr. 2007 Oct;53(5):331-7.