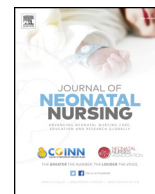




Contents lists available at ScienceDirect

Journal of Neonatal Nursing

journal homepage: www.elsevier.com/locate/jnn

Original Article

Study on effects of steroid on clinical course, short-term and long-term outcomes in neonates with meconium aspiration syndrome

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ARTICLE INFO

Keywords:

Meconium aspiration syndrome
Steroids
Neonates
Short-term outcome
Long-term outcome

ABSTRACT

The definite role of steroids in meconium aspiration syndrome (MAS), their safety and short-term as well as long-term outcomes are yet to be evaluated in large clinical trials; although some recent studies have yielded encouraging results. A randomized controlled trial was conducted over three years involving 275 neonates, where one group (n = 137) received intravenous (IV) methylprednisolone and nebulized budesonide along with the conventional management (IV normal saline and nebulized 3% saline), and the other group (n = 138) received conventional management only. These infants were followed up at 1, 3, and 6 months after discharge. We noticed a remarkable and statistically significant improvement in the clinical course including reduction in the Downes' score, oxygen dependency, the need of mechanical ventilation, and respiratory distress as well as a reduction in long-term complications including bronchopulmonary dysplasia, cerebral palsy etc.; in neonates receiving IV and nebulized steroid. We also did not observe any increased rate of sepsis, hypoglycemia, necrotizing enterocolitis in this group.

Introduction

Meconium aspiration syndrome (MAS) is a significant cause of neonatal mortality and morbidity, mainly in term and post-term infants. The incidence of meconium-stained liquor varies from 5% to 25% and nearly 10% of affected newborns develop MAS (Wiswell and Bent, 1993; Basu et al., 2007; Sivanandan et al., 2017). In spite of considerable improvement of antenatal obstetric care, a significant number of newborns develop MAS and throw challenges to the neonatologists. Steroids have a definitive role in the prevention of respiratory distress syndrome and intraventricular hemorrhage, but their use in the post-natal period is controversial (Tripathi and Saili, 2007). Though the mechanism of development of MAS still remains unclear, inflammation has a definite role in pathogenesis (Cleary and Wiswell, 1998; Soukka et al., 2002; Mokra and Mokry, 2011). Aspiration of meconium leads to activation of macrophages and diffuse infiltration of lung parenchyma by neutrophils. This, in turn, leads to an increase in pulmonary vascular permeability and exudate formation leading to a decrease in the amount of surfactant and lung compliance. As steroids inhibit different inflammatory mediators, henceforth, there is a pharmacological basis behind the thinking that steroids may be useful in the treatment of

MAS. Arguments are still there regarding the use of steroids and their role in MAS (Tripathi and Saili, 2007). The result of studies done in earlier years was totally disappointing but later studies, from different parts of the world, showed the benefits of steroids in the treatment of MAS (van den Anker, 1994; da Costa, 2001; Tripathi and Saili, 2007; Basu et al., 2007). Various newer management modalities for MAS like extra-corporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO) etc., are available but those are difficult to afford for a developing country like India. In order to obtain convincing data on the role of steroids in MAS so as to recommend or not to recommend them, more and more trials are required (Ward and Sinn, 2003). Neither of the previous studies had methodically tried to evaluate the use of methylprednisolone and nebulized steroids nor had they estimated the rate of future complications in full-term babies with MAS (Tripathi and Saili, 2007). As there is paucity of information regarding the role of steroids in MAS, choice of steroid derivative, their dose schedule and route of administration (Mokra and Mokry, 2011); in this study we have tried to find out the efficacy of steroids in management of MAS and the complications of their use, if any.

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<https://doi.org/10.1016/j.jnn.2018.06.001>

Received 29 March 2018; Received in revised form 24 May 2018; Accepted 6 June 2018

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Materials and methods

Study place and period

A randomized controlled trial was conducted in the Sick Newborn Care Unit (SNCU) and Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics of Burdwan Medical College between April 2014 and March 2017.

Ethical consideration

We obtained the ethical permission from the Institution Ethics Committee (IEC) [Memo no- BMC/CREC/33/2014 dated 03/01/2014] before the initiation of the study.

Inclusion and exclusion criteria

In our study, MAS was diagnosed on the basis of the following criteria – i) infants born through meconium stained amniotic fluid (MSAF) and having a birth weight of ≥ 2 kg, ii) detection of meconium below the vocal cord on endotracheal tube (ET) suctioning, iii) initiation of respiratory distress within 6 h of birth, iv) presence of infiltrations, hyperinflation and atelectasis in chest radiograph, and v) exclusion of other possible causes of respiratory distress in newborn. Preterm or newborns with intrauterine growth restriction (IUGR), neonates with major congenital malformations, whose parents did not want to participate in the study, and who died during the early neonatal period were excluded from the study.

Study procedure

Newborns who met the criteria were randomly assigned into two groups, newborns of group A received IV methylprednisolone (injection Solu-Medrol) in a dose of 0.5 mg/kg/day in 12 hourly divided doses and budesonide respirator solution (i.e. Budesonide respirator suspension 0.5 mg in 2.5 ml of normal saline) by nebulization every 12 hourly for 7 days, in addition to conventional management and group B, received conventional management of MAS [IV normal saline and nebulization with 3% normal saline (3% NaCl)] as placebo.

In the mentioned time period, 321 newborns were admitted with the diagnosis of MAS and 46 of them were excluded from the study due to different reasons. The rest of them were randomly divided into group A consisting of 137 newborns and group B consisting of 138 newborns (Fig. 1).

Data were collected using a pre-tested, pre-designed and semi-structured schedule by the resident doctors who were not aware of the purpose of the study. Respiratory distress was measured by Downes' score (Wood et al., 1972; Mathai et al., 2007). Both the group had a comparable Downes' score on the Day 1. Downes' score was calculated on each day. After discharge, the infants were followed up at 1, 3, and 6 months for any complications. The same stethoscope was used throughout the study period for the purpose of quality control.

Statistical analysis

Collected data were entered into Microsoft Excel worksheet. Shapiro-Wilk test was used to measure the skewness of the data which reveals that data were skewed. Hence median was used as a measure of central tendency and inter-quartile range (IQR) as a measure of dispersion. A non-parametric test was used for testing the significance of difference between two groups. A binary logistic regression model was created using long-term complication/death as an outcome variable. Kaplan-Meier survival analysis was also done. $P < 0.05$ was taken as statistically significant. All the statistical analysis was done using SPSS software version 20.0.

Results

Mean gestational age of the neonates in the study group was 38.5 ± 1.0 weeks. Mean birth weight of the neonates in the study group was 2.4 ± 0.2 kg. There was no significant difference between group A and B in gestational age, sex, birth weight and mode of delivery (Table 1).

With these similar baseline characteristics, both the group had similar Downes' score on day 1. But on the subsequent days, group A showed a less median Downes' score than group B. This difference was significant. The intervention group had a lower oxygen dependency, required less time for the obliteration of respiratory distress, required lesser time on mechanical ventilation and experienced a lesser duration of hospital stay. All these observations were significant statistically. Long-term complications like bronchopulmonary dysplasia, cerebral palsy etc. were also significantly lower among group A (Table 2). Binary logistic regression analysis showed that members of group A were 0.59 (95% CI: 0.51–0.68) times less likely to suffer from complication. This finding was significant statistically. The Kaplan-Meier analysis¹ (Fig. 2) also revealed a statistically significant increase in the hazards of the newborns of group B compared to group A. There were no significant differences in the incidence of sepsis and necrotizing enterocolitis in group A and Group B.

Discussion

In our study, we found that the use of intravenous and nebulized steroids significantly reduced the Downes' score, oxygen dependency, need of mechanical ventilation, respiratory distress, and long-term complications. Use of systemic steroids for MAS was evaluated by Frantz et al. (1975). Later Yeh et al. (1997) found hydrocortisone ineffective in the treatment of MAS. Wu et al. (1999) also failed to demonstrate any efficacy of dexamethasone in the treatment of MAS. But, Andrew and Davey (1995) and Khan et al. (1999) demonstrated the efficacy of dexamethasone in the management of MAS. Frantz et al. (1975), Kirimi et al. (2003) also observed decreased microscopic changes in lung tissue among steroid treated individuals. Several modes of actions of steroids are being proposed in the recent years that include inhibition of production pro-inflammatory cytokines and inflammatory mediators. Soukka et al. (1997) found methylprednisolone has a protective effect in MAS. Halliday et al. (2001) and Li et al. (2001) also observed the protective efficacy of budesonide. Their findings were similar to the observations of us. We found that oxygen dependency is significantly lesser among newborn treated with steroid. Wu et al. (1999) also similarly described that the time required to wean infant from oxygen is less among newborn treated with steroids but their observation was not significant statistically. On the contrary, Frantz et al. (1975) found that use of hydrocortisone leads to longer time requirement in weaning infant off from oxygen. A recent study by Garg et al. (2016) concluded that budesonide nebulization in MAS culminates in a considerable overall improvement in general as well as respiratory condition of the newborn like lesser oxygen requirement, prompt settlement in respiratory distress, and early improvement of Downes' score; in the initial part but the final outcome remains unaltered. Some authors found a higher incidence of sepsis, hypoglycemia and cerebral palsy among steroid treated individuals. But we did not observe any significant rise of these complications among steroid-treated groups rather noticed a decrease in the incidence of long-term complications.

Though the sample size meets statistical requirement and more compared to previous studies, recruitment of more subjects and multi-centric study should be conducted before recommending steroids as a

¹ Blue line represents group B & green line represents group A showing much more cumulative hazard in group B.

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