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Steroids in full term infants with respiratory failure and pulmonary hypertension due to meconium aspiration syndrome

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Abstract Persistent pulmonary hypertension of the newborn (PPHN) due to meconium aspiration syndrome (MAS), has a high morbidity and mortality especially in centres with limited access to extra-corporeal membrane oxygenation or nitric oxide therapy. In such a setting, we conducted a pilot study to evaluate the effect of dexamethasone on severe respiratory failure with PPHN due to MAS with a view to exploring possible justification for randomised controlled trials in similar patients. We prospectively managed a consecutive case series of 14 infants over a 3-year period with the above mentioned diagnosis, who were ventilated and with an oxygenation index >25. Dexamethasone was commenced in a dose of 0.5 mg/kg per day and given for up to a maximum of 9 days in a reducing schedule. Differences between time points were analysed using analysis of variance for repeated measures. The mean age of commencing dexamethasone was 79.9 h. There was a rapid, significant improvement ($P < 0.05$) in the respiratory status in 13 of these infants after commencing dexamethasone, allowing weaning from the ventilator and eventual extubation at a mean age of 8.7 days. One infant died. Two infants had infective episodes.

Conclusion Dexamethasone, if started early in infants with respiratory failure and persistent pulmonary hypertension of the newborn due to meconium aspiration syndrome may be effective in improving gas exchange, and possibly avoiding extra-corporeal membrane oxygenation. A randomised controlled trial of using dexamethasone early in similar patients and setting is warranted.

Key words Dexamethasone · Meconium aspiration syndrome · Persistent pulmonary hypertension of the newborn

Abbreviations *ECMO* extra-corporeal membrane oxygenation · *HFOV* high frequency oscillatory ventilation · *MAP* mean airway pressure · *MAS* meconium aspiration syndrome · *OI* oxygenation index · *PPHN* persistent pulmonary hypertension of the newborn

Introduction

Severe respiratory failure with persistent pulmonary hypertension (PPHN), due to meconium aspiration syndrome (MAS), in the full term newborn constitutes a very sick population of infants with significant mortality and morbidity. Tolazoline, magnesium sulphate infusions [1], surfactant therapy [11], conventional and high frequency ventilation have been used with varying success. Extra-corporeal membrane oxygenation (ECMO) [3, 14] and more recently nitric oxide therapy [13, 16] have been shown to be effective but not widely available in all centres, and it is difficult and hazardous to transport these patients over long distances.

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Exposure to meconium causes a profound pulmonary inflammatory response leading to lung injury [6, 15], in part mediated by inflammatory cytokines like tumour necrosis factor-α, interleukin 1β and interleukin 8 [9]. These cytokines may also be a factor in pulmonary vasoconstriction which leads to PPHN and worsening of the respiratory failure [10]. Further lung damage and worsening of the lung pathology may also be caused by barotrauma and oxygen toxicity due to mechanical ventilation and supplemental oxygen. Systemic steroids are known to reduce oedema and inflammation, which occurs with lung injury due to its potent anti-inflammatory effects. It also suppresses the formation of thromboxane and PGF2α which mediate pulmonary vasoconstriction [4]. This effect is achieved by inhibition of the enzyme phospholipase A2.

In a centre which has no access to ECMO, or nitric oxide therapy, we performed a pilot trial using dexamethasone in infants with MAS and PPHN with a view to assessing weaning from the ventilator and prevention of death.

Subjects and methods

The study was conducted over a 3-year period between January 1996 and December 1998 at the Royal Hospital which is a tertiary referral centre for neonates in the Sultanate of Oman with a birth rate of about 50,000 infants annually. We enrolled neonates prospectively into the trial who met all of the following entry criteria: (1) gestational age $\geq$ 37 weeks, (2) birth weight $\geq$ 2000 g, (3) MAS, (4) respiratory failure requiring ventilation with an oxygenation index (OI) $>$25, (5) PPHN as demonstrated clinically and on echocardiography within the first 24 h of life, (6) absence of sepsis or infective pneumonia at enrolment and (7) absence of major congenital malformations.

MAS was considered present if there had been thick particulate meconium stained liquor or thick meconium visualised and aspirated below the vocal cords, clinical features of respiratory distress and a chest X ray compatible with MAS as reported by a radiologist. Intubation and ventilation was commenced on those infants with respiratory failure ($PaCO_2$ $>$ 55 mm Hg; PaO_2 $<$ 50 mm Hg in 60% supplemental oxygen), or who demonstrated PPHN and oxygen saturation lability, or who had severe respiratory distress at birth. All ventilated infants were initially commenced on conventional pressure support ventilation. Dexamethasone was commenced between 48 to 96 h of life at a dose of 0.5 mg/kg per day (two divided doses) i.v., as a bolus injection over 5 min, and continued for up to a maximum of 9 days on a reducing schedule in 3-day blocks (0.5 mg/kg per day for 3 days; 0.25 mg/kg per day for 3 days and 0.125 mg/kg per day for 3 days). Criteria for commencing dexamethasone was the inability to wean from the ventilator or a worsening OI over two or more data point periods of 8 h each, i.e. 16 h. Prophylactic antibiotics were not administered and used only if septicaemia or pneumonia were suspected.

Our ventilatory management strategy for infants with PPHN is to achieve a pH of $>$7.45; $PaCO_2$ in the range of 25–35 mm Hg and PaO_2 $>$ 50 mm Hg. High frequency oscillatory ventilation (HFOV) is used if there is a failure of or worsening of ventilatory parameters while on conventional ventilation. The child is commenced on a mean airway pressure (MAP) 2 cm above that while on conventional ventilation and the amplitude is adjusted until the chest wall is seen to move. Blood pressure is supported with crystalloid or colloid volume replacement and inotropes (dopamine and or dobutamine) to maintain a systolic blood pressure higher than the pulmonary artery pressure measured on echocardiography or $>$70 mm Hg (whichever is greater) as far as is practically feasible. This is done prior to the use of dexamethasone.

PPHN was considered present if preductal arterial saturations were $\geq$ 10% higher than the post-ductal saturation and echocardiography confirmed absence of congenital heart disease and evidence of PPHN (right to left ductal or persistant foramen ovale shunting with evidence of high right ventricular/pulmonary artery pressure on Doppler examination). Echocardiography was done within the first 24 h of life. Chronic lung disease was considered if the child remained ventilated or oxygen dependant at 28 days postnatally and had a compatible radiological picture. Variables routinely monitored for infants on the ventilator were recorded from the flow sheet. Blood gases were done at least every 4 h, as is routine policy on the unit for these sick infants. OI was calculated from the ventilatory variables and blood gases according to the following formula:

$$\mathrm{OI} = \frac{\mathrm{MAP} \times \mathrm{FiO_2}}{\mathrm{PaO_2}} \times 100$$

Where MAP = mean airway pressure; FiO_2 = fraction of inspired oxygen content (range 0.21–1.0); PaO_2 = post-ductal PaO_2. Surfactant was administered if the FiO_2 was $>$60% and the MAP was greater than 7 in the first 24 h of life. The natural surfactant Survanta was used and was given according to the manufacture's recommendation and at least 16 h before commencement of dexamethasone.

Neurodevelopmental follow-up at 6 months and 18 months of age will be performed. The protocol and study design were approved by an institutional review board and informed consent was obtained from the parents.

Statistical analysis

This being a pilot trial, no sample size calculation was performed. There was no control group. The OI against time was analysed by ANOVA for repeated measures. Post hoc analysis was done using a Bonferroni correction. A P value of <0.05 was considered statistically significant.

Results

A total of 14 neonates were enrolled over a 3-year period from January 1996 to December 1998. No infants were excluded who met our predefined criteria. Initial enrolment characteristics are given in Table 1. Treatment modalities tried prior to commencement of dexamethasone, the respiratory parameters and outcome variables are shown in Table 2.

The OI for 24 h prior to and for 48 h after commencing steroids is shown in Fig. 1. Significant reduc-

Table 1 Initial characteristics of neonates enrolled

Characteristics of enrolled neonates		
Total (n)		14
Sex	Male	6
	Female	8
Birth	Inborn	4
	Referred	10
Gestation (weeks)	Mean ($\pm$SD)	39.3 (1.6)
	median (range)	40 (36–42)
Birth weight (g)	Mean ($\pm$SD)	3369 (518)
	median (range)	3300 (2610–4310)
Type of delivery	Vaginal	9
	Emergency caesarean section	5

Table 2 Therapies and outcome measures

Therapies and outcome	
Survanta used	10
Magnesium sulphate infusion	2
HFOV administered	4
Total days ventilated – mean (±SD) median (range)	8.7 (3.6) (5–16)
Total days on oxygen – mean (±SD) median (range)	12.4 (3.9) (6–19)
Death	1
Chronic lung disease	0
Steroids commenced (mean h of life) (range)	79.9 (65–108)
Infectious episodes:	Septicaemia Infective pneumonia
Hypertension requiring therapy	0

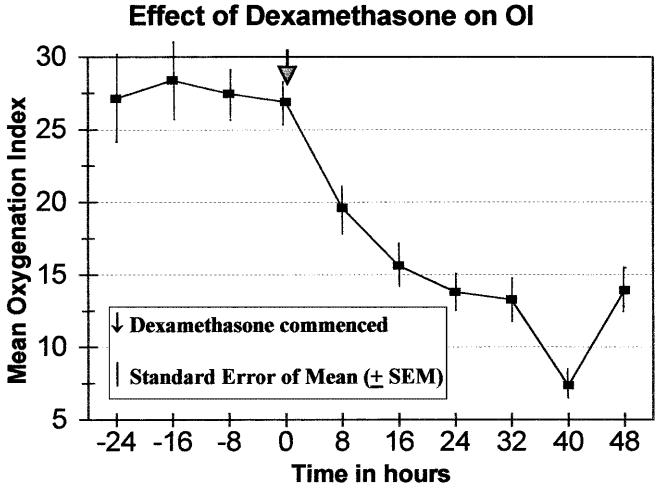

Fig. 1 Effect of dexamethasone on OI

tion compared to the previous time point is seen at 8, 16, 32 and 40 h after commencement of steroids. Rapid weaning was possible as is shown in the graph of OI plotted against time.

There were no infants with hypertension (systolic BP > 100 mm HG on two consecutive occasions 6 h apart) or hyperglycaemia (blood glucose > 10 mmol/l) requiring therapy. One infant developed septicaemia and one an infective pneumonia. Some slowing (< 100/min) of the baseline heart rate was seen in six of the infants after commencing dexamethasone. There was a drop in weight of an average of 7% after treatment was commenced as measured on day 1 and day 10 of starting dexamethasone. This may have been in part related to loss of oedema fluid due to improvement, or true weight loss or a combination.

Discussion

We conducted this study, as we presently have no access to ECMO or nitric oxide therapy. A review of our data in the 2 years preceding the study showed that of 19 patients with respiratory failure who had OIs >25 for at least two data points 4 h apart in the first 24 h after admission, ten reached ECMO criteria (OI > 35 for 8 h) and eight of these died.

In a piglet model of MAS, Khan and colleagues [12] found dexamethasone improved pulmonary compliance and decreased oxygen requirements. Soukka et al. [17] also showed that methylprednisolone reduced the pulmonary hypertension in MAS in piglets. Davey et al. [7] reported their initial results from a randomised controlled trial of dexamethasone in MAS in infants. They showed less airway white cell counts in the dexamethasone group suggesting a decreased pulmonary inflammatory response. There has been only one other report to the best of our knowledge on similar patients. Barr [2], reporting from Australia, showed in a small population of full term infants with respiratory failure of diverse aetiology and pulmonary barotrauma that there was a significant improvement in oxygenation and rapid weaning from mechanical ventilation. We chose infants with an OI of >25 as they represent a sick population of infants with a potential for high morbidity and mortality. Dexamethasone was considered only after 48 h as other therapies like surfactant, magnesium sulphate infusion and HFOV were tried prior to its use.

Our results show a rapid weaning in these sick infants, within 8 h of commencing intravenous dexamethasone. Thirteen of the fourteen infants improved. One infant showed no response and developed progressive respiratory failure and died. It could be argued that the beneficial effects seen could be attributed to either surfactant (Survanta) or magnesium sulphate infusion. However, the time between the last dose of surfactant or magnesium sulphate and commencement of dexamethasone was 16 h. da Costa et al. [5] have shown that the maximum effect of Survanta occurs within the first 6 h. The improvement also seems to be temporally related to dexamethasone administration. An apparent worsening in the OI is seen between the 40 and 48 h time points. On careful analysis of the patients it was felt that there was overaggressive weaning at the 32 to 40 h time point and this led to some worsening of the oxygenation as reflected in the arterial blood gases and OI, causing the ventilatory parameters to be increased again. Subsequently these patients (except for the one who died) weaned rapidly and were extubated at a mean age of 8.7 days.

No infant required antihypertensive therapy. We treat hypertension in full term babies if the systolic blood pressure is $\geq$ 100 mm Hg on two or more occasions 4 h apart. Transient hyperglycaemia was observed which resolved on reduction of steroid dose. None required stoppage of steroids or institution of insulin therapy. One infant developed septicaemia on day 6 and another infective pneumonia on day 8, which was treated with appropriate antibiotics. This not being a randomised controlled trial, but a pilot study, there was no control group. Ventilatory strategies are often crucial in the management of these infants and only 31%

received a trial of HFOV. In all these infants, no improvement was seen. Recent reports have suggested that dexamethasone when used in preterm infants to prevent the development of chronic lung disease may increase the incidence of intestinal perforations [8] (in this small series, none were seen in our patients) and cerebral palsy [18]. We, however, used dexamethasone as a rescue therapy in a population of infants with a high predicted mortality. Developmental follow-up studies are planned at 8 months and 18 months of age.

We have shown in a sick population of infants with respiratory failure due to MAS that dexamethasone can prevent worsening of the respiratory failure and the development of ECMO criteria. This may be a useful modality of treatment in centres with limited access to ECMO or inhaled nitric oxide. We feel that a randomised controlled trial in similar infants is warranted.

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