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Management of Neonatal Emergencies: Current Evidence Clinical Question 2: Is Surfactant Useful in Treatment of Meconium Aspiration Syndrome?

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Clinical scenario

You are a neonatology resident called to attend a term normal delivery. As you reach the delivery room, you are informed that the amniotic liquor is meconium stained. You anticipate the complications and prepare for delivery. The baby does not cry at birth. Baby is resuscitated with direct endo-tracheal suctioning with subsequent requirement of ventilation. He is shifted to NICU and put on mechanical ventilation. The ventilator setting requirement is high. X ray done is corroborative with meconium aspiration syndrome. You are worried about the ventilator settings Your junior resident asks you if there is any role of surfactant replacement therapy in this neonate as she has read that meconium causes inactivation of surfactant and leads to secondary surfactant deficiency. She has the following questions:

1. Is there a role of surfactant administration in neonates with meconium aspiration syndrome?
2. What is the appropriate dosage and method of administration?
3. Are there any studies which provide evidence as to the benefit of surfactant in babies with meconium aspiration syndrome?

You recall reading the literature on this but are not sure of the benefit or harm of surfactant administration in meconium aspiration syndrome. You tell her that you will respond after reviewing the available literature.

Background

Meconium aspiration syndrome (MAS) is an important cause of respiratory distress in near term and term infants, affecting nearly 5-10% of infants born with meconium stained liquor.[1,2] Despite advances in treatment and advent of newer and alternative therapies like surfactant administration, inhaled nitric oxide (iNO), liquid ventilation, high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO), treatment of MAS remains difficult, with considerable morbidity and mortality.[2,3] The pathogenesis and pathophysiology of meconium aspiration syndrome is complex with contributing factors such as mechanical obstruction of airways, chemical injury to alveolar epithelium, impaired gas exchange and persistent pulmonary hypertension.[4,5] Meconium also damages the alveolar epithelium and inhibits pulmonary surfactant function; this inhibitory action is concentration dependent.[6,7] Hence surfactant replacement has been used in trials to counteract this affect. There are two ways of replacing surfactant, one as a bolus dose and the other as lung lavage with diluted surfactant. Bolus surfactant administration has

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been used in few clinical trials to treat MAS with a view to replace natural surfactant. [8,9] Lung lavage with diluted surfactant has been proposed as an alternative method of surfactant use for MAS, which could, theoretically, alter the natural course of MAS by enhancing the removal of meconium from the airways and hence augmenting surfactant function. [10] This clinical query tries to review the evidence, or lack thereof, for the use of bolus and lung lavage surfactant in MAS.

Evidence

Till date there is a Cochrane review[11] (including four randomised trials) on bolus dose of surfactant in MAS and a systematic review of lung lavage with diluted surfactant along with few animal studies. Let's review the evidence in detail.

1. *Bolus dose of surfactant*

Cochrane review

The Cochrane Review (2009)[11] by El Shahed *et al* included four randomized controlled trials-Findlay *et al* (1996)[8], Lotze *et al*(1998)[3], Chinese Collaboration Study (2006)[9] and Maturana *et al* (2005).[13] The meta-analysis of these four trials which enrolled 326 infants showed no statistically significant effect on mortality [relative risk 0.98 (95% CI 0.41, 2.39)]. The risk of requiring extracorporeal membrane oxygenation was significantly reduced in a meta-analysis of two trials (n = 208); [relative risk 0.64, 95% CI 0.46, 0.91]; number needed to treat; NNT: 6 (95% CI 3, 25). One trial (ref) (n = 40) reported a statistically significant reduction in the length of hospital stay [mean difference: - 8 days (95% CI -14, -3 days)]. There were no statistically significant reductions in any other outcomes studied (duration of assisted ventilation, duration of supplemental oxygen, pneumothorax, pulmonary interstitial emphysema, air leaks, chronic lung disease, need for oxygen at discharge or intraventricular haemorrhage).

Randomized Controlled Trials

Initial uncontrolled studies of bolus surfactant administration in infants with MAS provided some support to its use. Findlay and co-workers[8] conducted a single-centre randomised controlled trial of surfactant therapy in 40 ventilated infants with MAS. Entry criteria included a mean airway pressure (PAW) >7cm H_2O, and an alveolar-arterial oxygen ratio of <0.22, with enrolment occurring in all cases by 6 hours of age. Three doses of beractant (150 mg/kg) were administered over 20 minutes *via* a sideport on the endotracheal tube six hours apart. Surfactant treated infants showed a reduction in mean hospital stay as well as need for ECMO. There were no other differences in the outcome measures.

Lotze *et al*[12] conducted a randomized controlled trial including mechanically ventilated term infants needing 100% oxygen and having an oxygenation index (OI) of between 15 and 40 upto 120 hours of age. Of the 328 infants enrolled, 168 had a primary diagnosis of MAS. Four doses of beractant was given, each 100 mg/kg, as bolus doses via the endotracheal tube. Surfactant-treated infants showed a decrease in the requirement for ECMO (37% vs 52%), but no reduction in pulmonary complication or other outcomes.

Chinese collaborative Study group[9] performed a study of 19 Neonatal Intensive care units.[4] Sixty-one term infants with severe MAS were randomly assigned to either a surfactant or a control group within 36 h after birth. The infants in the surfactant group received an initial dose of porcine lung derived surfactant at 200 mg/kg, and repeated doses of 200, 100 and 100 mg/kg were given at 6–12 h intervals to a maximum of four doses if oxygenation index (OI) deteriorated by 2 from baseline. There was a trend for surfactant treated infants to have an improvement in arterial oxygenation compared to the control group. In comparison with the control group at 24 h, the surfactant group had a lower mean OI (8.1 vs 10.9), more infants with a 100%

increase of a/A PO2 (83% *vs* 48%, p50.01) over baseline, and a larger area under the curve for PaO_2/FiO_2 over baseline (3762+1877 *vs* 2715+1644 mmHg.h, p50.05). Repeated measures of these parameters were also in favour of the surfactant group. There were no differences in mortality, duration of mechanical ventilation and incidence of complications.

2. *Surfactant Lavage*

There has been interest in the possibility of introduced cleansing of the lung with fluids with favourable biophysical properties, such as surfactant. Two randomized controlled trials compared surfactant lavage with control infants and yielded inconclusive results. Dargaville *et al* have performed a multicentre collaborative trial [the LessMAS (Lavage with Exogenous Surfactant Suspension in Meconium Aspiration Syndrome)trial][15] which included 66 infants. Infants randomized to lavage received two 15-mL/kg aliquots of dilute bovine surfactant instilled into, and recovered from, the lung. Control subjects received standard care. The trial concluded that median duration of respiratory support was similar in both groups (5.5 versus 6.0 days, P = 0.77). Requirement for high frequency ventilation and nitric oxide did not differ between the groups. Fewer infants who underwent lavage died or required ECMO: 10% (3/30) compared with 31% (11/35) in the control group (odds ratio, 0.24; 95% confidence interval, 0.060-0.97).

Systematic review (Hyun Jin Choi et al 2012)[16] (Table 1& 2)

The authors conducted a meta-analysis by systematically reviewing the most up-to-date available evidence in the current literature to assess the effectiveness of surfactant lavage therapy for infants with MAS. A total 10 studies were included in the analyses: two RCTs and eight non randomised trials

Results of the meta-analysis

Surfactant lavage significantly decreased death or the need for ECMO in both RCTs (RR 0.34, 95% CI 0.11, 0.99) (table 1 and 2) and NRSs (RR 0.35, 95% CI 0.13, 0.94). All studies except one [22], in which more severe patients were involved in the treatment group at the baseline, consistently showed intervention-favourable results. No statistical heterogeneity was present in any of the meta-analyses. Funnel plot assessment did not reveal an indication for publication bias.

In the two RCTs, no treatment effect on the duration of supplemental oxygen was

Table 1: Comparison of the RCT's for surfactant lavage

Study (first author)	Study design	Study population	Baseline OI (i/c)	Mean timing of lavage (h after birth)	Total lavage volume	Aliquot volume	Lavage fluid conc
Wiswel 2002	RCT	(i) n = 15 (c) n = 7	average 12	14–15	48 ml/kg	8 ml/kg	Lucinactant 2.5–10 g/ml
Dargaville 2011	RCT	(i) n = 30 (c) n = 35	average 25	14	30 ml/kg	15 ml/kg	Beractant 5 mg/ml

Table 2: Summary of the Meta-analysis of the RCT Surfactant Lavage

Outcome	Studies	Patients (i/c)	RR (95% CI)
Death or need for ECMO	2	45/42	0.34 (0.11–0.99)
Mortality (overall)	1	30/35	0.44 (0.13–1.50)
Need for ECMO	2	26/21	0.27 (0.04–1.86)
Pneumothorax	2	45/42	0.39 (0.08–1.95)

RCT: Randomized controlled trial; ECMO: Extra corporeal membrane oxygenation; RR = risk ratio; CI = confidence interval

observed, while in the NRSs significant heterogeneity was present

Animal studies

The physiological effect of exogenous surfactant therapy has been investigated in animal models of MAS. Study done on rabbits (17) show improved oxygenation, however in several cases the oxygenation effect was transient or absent. A more pronounced physiological response was noted with a 200 mg/kg surfactant dose (compared with 100 mg/kg) in the rat MAS model but not in the rabbit model. The improvements in gas exchange have been assosciated with concomitant improvements in pulmonary mechanics and, where measured, with the epithelial injury and proteinaceous exudation.[17]

Discussion

The available evidence seems to come from one meta-analysis which does not favour the use of surfactant to reduce mortality in MAS, but favours reduction in need of ECMO. Other evidence comes from the lavage done with diluted surfactant. But there are concerns regarding the studies and accepting the validity of the results. The concerns include:

1. *Inclusion Criteria:* Although all the randomized controlled trials cited included infants with severe MAS requiring mechanical ventilation, they used diverse criteria for inclusion in the study. As such it becomes difficult to ascertain the patients that will benefit from the use of surfactant. It is also not clear if moderate MAS would benefit from surfactant usage or not. Hence the need for strict and similar inclusion criteria needs to be emphasied for future trials
2. *Timing and Dosage of surfactant:* Two of three trials used multiple doses of surfactant in all infants while the Chinese group used a single dose, with further doses being used in patients who showed deterioration. The dosage used for a single administration also differed between various studies. The effect of surfactant seen in a particular trial may reflect the cumulative dosage used rather than any single dose. The timing of surfactant administration was also late in the latter (up to 36 hours), while other trials initiated treatment with surfactant by 6 hours. Since MAS is a progressive disease, it follows that patient who are initiated early on a particular treatment might show greater benfit.
3. *Type of Surfactant and method of administration:* All these trials used lung mince surfactant (beractant or poractant), but while Findlay et al administered surfactant via infusion over 20 min, others gave it as bolus doses via endotracheal tube. The administration of surfactant by infusion may be associated with relatively poor distribution of surfactant.[8]

The heterogeneity in dosage of surfactant, type of surfactant, timing of first dosage, number of doses used, dosing frequency, mode of surfactant delivery and the quality of preparation might thus, influence the response generated.

The supportive care available at various centres also varied greatly, with ECMO being available at some centres and not others. This might influence the mortality rate as well as outcome measures.

Conclusion

The available data gives some support for the use of bolus surfactant therapy in severe MAS, particularly in resource-poor settings where ECMO and other measures such as high frequency ventilation may not be readily available. However, the patient population that would receive the greatest benefit, as well the optimum timing for initiation of treatment, method and dosage for administration and the

number of doses still needs to be determined. Lung lavage using surfactant is another upcoming intervention which needs to be subjected to more trials before any recommendations can be made.

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