Treatment of Severe Meconium Aspiration Syndrome with Dilute Surfactant Lavage

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Background and Purpose: Despite the development of new adjuvant therapies, meconium aspiration syndrome (MAS) remains a serious respiratory disorder in neonates. Surfactant inactivation by meconium can be overcome by use of exogenous surfactant. This study sought to assess the efficacy and safety of dilute surfactant lavage at 2 different concentrations to treat severe MAS.

Methods: We retrospectively reviewed the charts of all term infants with a diagnosis of MAS who had an oxygenation index (OI) > 20 during a 2-year period. Tracheobronchial lavage was performed with a dilute surfactant suspension (5 mg/mL or 10 mg/mL) to reach a total dose of 60 to 70 mg/kg of phospholipid, administered in aliquots of 2 mL.

Results: The records of 22 patients were reviewed, of whom 12 had undergone lavage. These patients were subdivided into low-concentration (surfactant concentration, 5 mg/mL; n = 6) and high-concentration (surfactant concentration, 10 mg/mL; n = 6) subgroups. There were no significant differences in demographic characteristics between these 2 subgroups. The lavaged infants had a significantly higher arterial partial pressure of oxygen (PaO_2) 24 hours after lavage than the infants without lavage (178.3 mm Hg *vs* 80.6 mm Hg, $p < 0.05$). The incidence of pneumothorax (1/12 *vs* 7/10, $p < 0.05$) and requirement for inhaled nitric oxide (5/12 *vs* 9/10, $p < 0.05$) were significantly lower in the lavaged group. All infants tolerated the procedure well except for 2 with transient complications. There were no significant differences in duration of lavage, response and complications between subgroups lavaged at low and high surfactant concentration.

Conclusions: Early lavage with dilute surfactant solution at a phospholipid concentration of either 5 mg/mL or 10 mg/mL is effective for the treatment of severe MAS. Further large-scale, prospective, randomized, controlled trials are necessary to establish the optimal dose, concentration, surfactant product, and instillation method of this treatment before it can be recommended for routine use.

Key words: Bronchoalveolar lavage; Infant, newborn; Meconium aspiration; Pulmonary surfactants

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Intrauterine stress such as hypoxia, hypercapnia and acidosis may cause passage of meconium into the amniotic fluid. Approximately 10 to 15% of live births are born through meconium-stained amniotic fluid (MSAF).[1] Fetal gasping or deep breathing movements can result in aspiration of MSAF and cause meconium aspiration syndrome (MAS). A recent study in Hong Kong reported an incidence of MAS of 1.5% in all newborn infants, while severe MAS necessitating mechanical ventilation occurs in 1.8 per 1000 deliveries.[2] Delivery room management, including DeLee suctioning of the nasopharynx before delivery of the shoulders and immediate tracheal intubation with suctioning, is not entirely effective in preventing MAS.[3] MAS is often associated with persistent pulmonary hypertension of the newborn (PPHN), the most common condition requiring extracorporeal membrane oxygenation (ECMO) in neonates.[4] Unfortunately, ECMO is not readily available in many centers. Despite the development of new adjuvant therapies, such as high-frequency oscillatory ventilation (HFOV), surfactant, inhaled nitric oxide (iNO) and ECMO,[5] MAS is still a severe respiratory disorder in neonates.

The pathophysiology of MAS is complex and is characterized by chemical pneumonitis and mechanical obstruction of the airways leading to atelectasis, emphysema, and air trapping. In addition, meconium contains several components — such as cholesterol, free fatty acids, and bilirubin — that inhibit surfactant function.[6] Surfactant inactivation by meconium can be overcome by addition of exogenous surfactant, the rationale for this therapy in MAS.[7] Previous studies in animal models have suggested that surfactant lavage

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therapy effectively removes meconium from the airway, resulting in prompt clinical improvement.[8,9] Ogawa et al[10] as well as Lam and Yeung[11] reported successful treatment using dilute surfactant to lavage 4 and 6 infants, respectively, with MAS. We used an approach similar to that of Lam and Yeung in newborns with severe MAS. Because the optimal dose and concentration of dilute surfactant were not defined, we assessed the efficacy and safety of treatment of severe MAS with dilute surfactant lavage at 2 different concentrations.

Methods

Patients

We retrospectively reviewed the charts of patients treated from July 2000 to June 2002 who met the following enrolment criteria: 1) term infants with a diagnosis of MAS; 2) oxygenation index (OI) > 20 at least once during the first 12 hours after admission; and 3) absence of congenital heart disease, diaphragmatic hernia, or lethal congenital anomaly.

From July 2000 to June 2001, we used a surfactant concentration of 5 mg/mL. Because lavage therapy is a relatively invasive procedure, we shortened the duration to avoid complications by changing the surfactant concentration to 10 mg/mL from July 2001 to June 2002. Patients undergoing lavage were therefore analyzed according to low-concentration and high-concentration subgroups. The lavaged group was compared with a group of infants with MAS during the 2-year study period whose parents did not consent to the lavage procedure.

Dilute surfactant lavage treatment

Surfactant suspensions for lavage were prepared by suspending surfactant [Survanta (Ross laboratories, Ohio, USA), 25 mg phospholipid/mL] in normal saline at a phospholipid concentration of 5 mg/mL in the first year, and 10 mg/mL in the second year. Tracheobronchial lavage was performed with a dilute surfactant suspension to deliver a total dose of 60 to 70 mg/kg of phospholipid. The amount of lavage fluid used was equivalent to 12 to 14 mL/kg in the low-concentration subgroup and 6 to 7 mL/kg in the high-concentration subgroup. The patients were not sedated or paralyzed during the lavage procedure. They were placed in 1 of the 4 standard positions for surfactant replacement therapy (SRT). Lavage fluid was administered in aliquots of 2 mL through the side hole on an endotracheal tube adapter. They were then manually ventilated until the O_2 saturation was > 90%. After each aliquot, suctioning was performed with an 8 Fr feeding tube at a negative pressure of 100 mm Hg. Patients were changed to another position before the next aliquot administration. The procedure was stopped if desaturation, apnea, or bradycardia persisted and only resumed after vital signs returned to normal.

Monitoring

Arterial blood gas sampling was performed through an indwelling arterial line. Blood gas analysis was performed at 0 and 30 minutes after treatment and then once every 6 hours afterwards or when clinically indicated. The OI was calculated by a standard formula: $OI = MAP \times FiO_2 \times 100 \div PaO_2$.

Initial ventilatory management was undertaken with a conventional mechanical ventilator (intermittent mandatory ventilation). The ventilator parameters were based on the following settings: positive end-expiratory pressure, 5 cm H_2O; sufficient peak inspiratory pressure for lung inflation; and sufficient fraction of inspired oxygen to maintain O_2 saturation > 90%. These settings were adjusted depending on the clinical condition and results of the blood gas analysis. If gas exchange or oxygenation could not be achieved with conventional ventilation [PaO_2 < 50 mm Hg or arterial partial pressure of CO_2 ($PaCO_2$) > 65 mmHg], we switched to HFOV (Humming V, Metran Medical Instrument MFG. Co. Ltd, Japan). Chest radiographs were performed with a portable X-ray machine before and 6 hours after treatment. Echocardiogram was performed if PPHN was suspected after the lavage therapy. After obtaining informed consent from the parents, iNO therapy was initiated if the following criteria were met: 1) OI > 25 at least twice after enrolment or 2 hours after the lavage therapy and 2) PPHN was confirmed by the echocardiogram.

The dilute surfactant lavage therapy and iNO therapy protocols were approved by the ethics and medical research committee of our hospital. Wilcoxon rank sum test, chi-squared test, and Fisher's exact test were used for statistical analysis. A $p < 0.05$ was considered statistically significant.

Results

During the 2-year period, 22 patients met the enrolment criteria. Twelve infants underwent lavage, 6 in the low-concentration subgroup and 6 in the high-concentration subgroup. Ten patients who met the enrolment criteria had not undergone lavage because their parents could not afford the cost of the surfactant (Survanta). HFOV was used before lavage therapy in 4 patients (33.3%) in the lavaged group and all enrolled subjects eventually received HFOV due to poor oxygenation. The usage of HFOV began at a

Table 1. Clinical characteristics of infants with severe meconium aspiration syndrome.

Characteristic*	Non-lavaged group (n = 10)	Lavaged group (n = 12)
Gestational age (mean ± SD; weeks)	39.7 ± 1.6	39.3 ± 0.6
Birth weight (mean ± SD; g)	3229 ± 607	3069 ± 458
Males [n (%)]	6 (60)	6 (50)
Apgar score at 1 minute (mean ± SD)	6.4 ± 1.8	6.2 ± 2.8
Apgar score at 5 minutes (mean ± SD)	7.1 ± 1.7	7.3 ± 2.2
Vaginal delivery [n (%)]	5 (50)	6 (50)
Inborn [n (%)]	5 (50)	5 (42)
OI at study entry (mean ± SD)	31.4 ± 11.9	32.5 ± 18.5

* The *p* value was non-significant for all comparisons.
SD = standard deviation; OI = oxygenation index.

mean age of 6.1 hours in the lavaged group (range, 0.5 to 10.5 hours) and 6.4 hours in the non-lavaged group (range, 1.0 to 13 hours). The mean age at the time of HFOV was not significantly different between the lavaged and non-lavaged groups.

Table 1 shows the demographic characteristics of the subjects. There were no significant differences in gestational age, birth weight, gender, Apgar score, inborn or vaginal delivery rate between newborns with and without lavage. The fraction of inspired oxygen, mean airway pressure, and OI were also similar in the 2 groups before the lavaged group underwent therapy. There were no significant differences in these characteristics between the subgroups that received lavage at low and high surfactant concentrations.

The instillation of dilute surfactant began at a mean age of 5.2 hours in the low-concentration subgroup (range, 2 to 9 hours) and at 4.2 hours in the high-concentration subgroup (range, 2 to 7 hours). Infants in the high-concentration subgroup took a somewhat shorter time (mean, 36 ± 12 minutes) to complete the lavage procedure than infants in the low-concentration subgroup (mean, 42 ± 15 minutes), but this difference was not significant. All infants tolerated the procedure well, except for 2 who developed transient complications. One infant in the low-concentration subgroup developed desaturation that lasted more than 5 minutes with a lowest O_2 saturation of 60%. This infant recovered after continuous manual ventilation. One infant in the high-concentration subgroup had blood-tinged fluid suctioned after instillation, but the bleeding stopped spontaneously without any specific therapy.

Twenty four hours after lavage, the lavaged group of infants had a significantly higher PaO_2 than those who had not been lavaged (178.3 mm Hg *vs* 80.6 mm Hg, $p < 0.05$). In comparison with 3 patients (30%) in the non-lavaged group, only 1 patient (8.3%) in the lavaged group still had an OI > 20 at 48 hours after lavage or enrolment. Lavaged infants appeared to have a more rapid and sustained improvement in OI than those who did not undergo lavage (Fig.), but this difference was not significant. There was no significant difference in the fraction of inspired oxygen, mean airway pressure, and OI between the low and high lavage concentration subgroups.

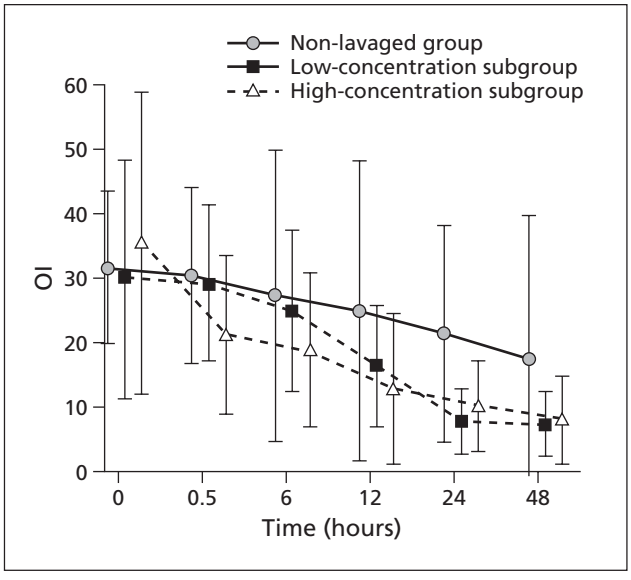

Fig. Change in oxygenation index (OI) during the first 48 hours after diagnosis of meconium aspiration syndrome (OI values expressed as mean ± SD).

Table 2 shows the outcome of the infants. Compared to newborns without lavage, the lavaged infants had a significantly lower incidence of pneumothorax (1/12 *vs* 7/10, $p < 0.05$) and requirement for iNO therapy (5/12 *vs* 9/10, $p < 0.05$). When administered, iNO therapy in the lavaged group was given after lavage therapy. While the mean duration of ventilation, O_2 administration, and length of hospital stay were slightly longer in the unlavaged infants, these differences were not significant. All 12 lavaged infants survived without sequelae. Two of the non-lavaged neonates died within 5 days after birth, and another 2 of these infants had seizures during the first day of life.

Discussion

MAS accounts for a large percentage of respiratory morbidity and mortality in newborn infants. Mechanical

Table 2. Characteristics of clinical course during hospitalization in infants with severe meconium aspiration syndrome (MAS).

Characteristic	Non-lavaged group (n = 10)	Lavaged group (n = 12)	*p* Value*
OI at 48 hours after lavage or diagnosis of MAS (mean ± SD) [range]	7.5 ± 5.0 (2.0–20.7)	17.3 ± 22.3 (2.5–76.5)	NS
iNO therapy required [n (%)]	9 (90)	5 (41.7)	0.03
Pneumothorax [n (%)]	7 (70)	1 (8.3)	0.006
Duration of ventilation (mean ± SD; days)*	10.4 ± 7.8	10.0 ± 4.9	NS
Duration of O_2 therapy (mean ± SD; days)*	15.3 ± 12	13.2 ± 5.4	NS
Duration of admission (mean ± SD; days)*	19.5 ± 9.7	17.6 ± 6.1	NS
Morbidity [n (%)]	2 (20)	0	NS
Mortality [n (%)]	2 (20)	0	NS

* Excludes 2 patients in the non-lavaged group who died by 5 days of age (n = 8).
OI = oxygenation index; SD = standard deviation; NS = not significant; iNO = inhaled nitric oxide.

obstruction of the airway is the most important pathophysiologic component of MAS, and may cause air leak. Meconium remaining in the airways may result in inflammation and surfactant dysfunction. An animal study showed that meconium migrates from the large to the small airways or alveoli due to its high tenacity.[12] Therefore, it is very important to remove meconium as early as possible to relieve mechanical obstruction and avoid migration of this potent surfactant inhibitor.

Encouraging preliminary reports of surfactant therapy have been published,[13,14] but little information is available about the optimal dose, method, and timing of instillation. There are several methods of surfactant therapy in the management of MAS, including SRT,[15] tracheobronchial lavage with a saline solution followed by surfactant administration,[16] and dilute surfactant lavage therapy.[11,17] In addition to requiring multiple, high doses for improvement, SRT also has the disadvantages of inability to remove meconium and administration of an excessive fluid load if multiple surfactant boluses are used. Saline lavage may result in worsening of respiratory failure and no improvement in oxygenation. The deterioration may be due to the removal of surfactant along with meconium, or the lavage itself may cause pulmonary edema and surfactant dysfunction.

Dilute surfactant lavage not only replaces the dysfunctional endogenous surfactant but also allows removal of meconium from the airways. This therapy is less costly, requires a lower volume load, has less risk of desaturation, and provides a more uniform distribution of surfactant when compared to SRT.[11] Balaraman et al demonstrated that all dilute surfactant preparations (Infrasurf, KL_4-surfactant, and Exosurf) were effective in reversing dysfunction after acute lung injury in a piglet model.[18] Herting et al suggested that Surfaxin (KL_4-surfactant) is better than Survanta for resisting meconium inactivation and lowering surface tension,[19] but only Survanta was available in our hospital during this study. Further testing is necessary to determine whether there are important differences between the various surfactant products available, including Survanta, Surfaxin, and Surfactant-TA.

Balaraman et al suggested that smaller doses of surfactant in the range of 20 to 40 mg/kg of phospholipid may be adequate when the administered surfactant is more uniformly distributed.[18] Most studies, however, have suggested that the inhibitory effect of meconium is dose dependent and that low concentrations of surfactant are relatively more sensitive to inhibition than high concentrations.[6,7] This finding has led to the proposal that meconium-induced surfactant inhibition can be overcome at sufficiently high surfactant concentrations. Our data suggests a total surfactant dose of 60 to 70 mg/kg of phospholipid may be sufficient to treat MAS and results in clinical improvement. This is compatible with the findings of Lam and Yeung, who used lower surfactant doses than recommended for SRT but still achieved favorable results.[11]

Ohama and Ogama found that lavage with Surfactant-TA at a concentration of 10 mg/mL washed out meconium very effectively and improved gas exchange in a rabbit model of MAS.[20] Lam and Yeung also suggested that larger volumes of instillation resulted in a higher chance of desaturation,[11] and this finding led us to increase the dilute surfactant concentration to 10 mg/mL during the second year of this study. Our data indicated that infants lavaged with surfactant at a concentration of 10 mg/mL had a slightly shorter procedure time than those lavaged with a 5-mg/mL solution, although this difference was not significant. Studies involving a larger sample size are needed to confirm this finding. The overall effects in our patients did not differ between the 2 concentrations.

Lavage therapy is a relatively invasive procedure compared to standard SRT, and there are concerns about its safety and potential to reduce complications.[21] Hypoxemia during the procedure may worsen pre-existing hypoxia. We prevented hypoxemia by ventilating the patients until the O_2 saturation was > 90% before and after instillation of each aliquot of lavage fluid. Large volumes of lavage fluid may injure

the pulmonary epithelium or lead to cardiopulmonary fluid overload, as with saline lavage. For this reason, we used a relatively small volume of lavage fluid (12 to 14 mL/kg in the low-concentration subgroup and 6 to 7 mL/kg in the high-concentration subgroup). Pulmonary hemorrhage may complicate lavage. Blood-tinged fluid was suctioned from 1 patient in the high-concentration subgroup, but the bleeding stopped spontaneously without specific therapy. In general, the procedure was well tolerated in most patients, and all 12 lavaged patients survived without short-term sequelae.

A limitation of our study was the small number of patients. Another was that we combined surfactant lavage therapy with other therapies to treat severe MAS. It is not possible to rely entirely on a single treatment modality or independent variable in clinical practice, even though this would be ideal for scientific investigation. The relative efficacy of surfactant therapy compared to, or in conjunction with, other approaches to treatment including iNO, liquid ventilation, and high frequency ventilation remains to be determined.

Conclusions

We conclude that early lavage with dilute surfactant solution at a phospholipid concentration of either 5 mg/mL or 10 mg/mL is effective for the treatment of severe MAS. This treatment significantly improved oxygenation and reduced the incidence of pneumothorax and the requirement for iNO therapy. Further large-scale, prospective, randomized, controlled trials are necessary to establish the optimal dose, concentration, surfactant product, and instillation method before the treatment can be recommended for routine use.

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