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Surfactant Lavage in a Piglet Model of Meconium Aspiration Syndrome[1]

MICHAEL S. PARANKA, WILLIAM F. WALSH, AND BRADLEY B. STANCOMBE

Department of Pediatrics, Wilford Hall United States Air Force Medical Center, Lackland Air Force Base, Texas 78236-5238

ABSTRACT. Meconium aspiration continues to be a major cause of morbidity and mortality in newborn infants and is one of the most common indications for extracorporeal membrane oxygenation. Lab studies have suggested that meconium inactivates surfactant and displaces surfactant from the alveolar surface. A recent report has suggested a clinical role for surfactant therapy in human infants with meconium aspiration. We evaluated the effect of surfactant (Survanta) lavage on a piglet model of meconium aspiration. Meconium pneumonitis was created by administration of 4 mL/kg of a 20% slurry of human meconium via endotracheal tube. Twenty-four newborn piglets were then randomly assigned to one of three groups: *1*) suction only ($n = 7$), *2*) saline lavage ($n = 5$), or *3*) surfactant lavage ($n = 7$). Five piglets were excluded from analysis due to death from pneumothorax during meconium administration ($n = 3$), death from pneumothorax during saline lavage ($n = 1$), and death from pneumothorax during surfactant lavage ($n = 1$). The surfactant group had a statistically significant ($p < 0.05$) improvement in arterial to alveolar oxygen ratio gradient *versus* both control groups for the first 3 h. The oxygenation index was statistically significant *versus* the suction only group at 1, 3, and 4 h. Surfactant lavage of meconium aspiration in piglets results in short-term improvement of oxygenation and warrants further study. (*Pediatr Res* 31: 625-628, 1992)

Abbreviations

MAS, meconium aspiration syndrome
PaO_2, arterial oxygen partial pressure
$PaCO_2$, arterial carbon dioxide partial pressure
a/A, arterial to alveolar oxygen ratio
OI, oxygenation index
FiO_2, fraction of inspired oxygen

MAS is associated with air leak, severe chemical pneumonitis, and pulmonary hypertension resulting in a neonatal mortality rate of up to 40% (1). Despite aggressive perinatal management, MAS continues to be a vexing problem. Over the past 5 years, meconium aspiration has been the most common pulmonary disease requiring extracorporeal membrane oxygenation in our institution (2).

The present management of the meconium-stained infant as suggested by Carson *et al.* (3) involves suctioning of the upper airway on the perineum before delivery of the thorax and then, if meconium is noted at the level of the vocal cords, direct suctioning of the trachea. Carson's group also found that, despite some removal of meconium, tracheobronchial lavage with saline in these same patients may actually enhance respiratory morbidity. The pathophysiology of MAS is complex, involving changes in compliance as well as airway resistance. Instillation of meconium into excised canine lungs has been shown to decrease lung compliance and functional residual capacity (4). Clark *et al.* (5) have demonstrated that meconium significantly alters surfactant function *in vitro*. These data suggest that meconium inactivates surfactant; therefore, direct instillation of an exogenous surfactant after meconium aspiration may improve surface active properties. Auten *et al.* (6), in a small, uncontrolled study in human infants with meconium aspiration, demonstrated significant improvements in PaO_2 and outcome after treatment with exogenous surfactant.

We hypothesized that the outcome of infants with MAS might be improved if surfactant was not only instilled, but also used as a lavage both to remove residual meconium from the airways and to ameliorate the effect of the washing out of natural surfactant. To test this hypothesis, we evaluated a piglet model of MAS to determine the short-term effect of surfactant lavage on gas exchange.

MATERIALS AND METHODS

We studied 24 1-wk-old piglets weighing 2–4 kg. Animals were sedated with ketamine hydrochloride (1 mg/kg) and then intubated with a 3.0 cuffed endotracheal tube. The animals were placed supine on Ohio warmers and maintained in this position throughout the study. A peripheral i.v. and femoral artery line were placed. Anesthesia was provided by fentanyl (5 μg/kg/dose), and paralysis maintained with pancuronium bromide (1 mg/kg/dose). Ventilation was performed using a Servo 900-C volume ventilator (Siemans-Elema, Solna, Sweden). All animals were maintained on 100% FiO_2 at a ventilator rate of 40 with positive end expiratory pressure of 5 cm H_2O and inspiratory time of 0.4 s. A tidal volume of 10–15 mL/kg was used to maintain the $PaCO_2$ between 4.67 and 6.67 kPa (35 and 50 mm Hg) throughout the protocol.

After baseline blood gas measurements, all animals were given 4 mL/kg of a 20% human meconium slurry via endotracheal tube. The goal was to reduce the PaO_2/alveolar PO_2 (a/A) gradient to < 0.2. We defined alveolar PO_2 as $FiO_2 \times 713 - PaCO_2$. Repeat doses of meconium were administered as necessary to achieve an a/A gradient < 0.2. The animals were then randomized into one of three treatment groups: group I, suction only; group II, saline lavage; and group III, surfactant lavage. Group I received tracheal suctioning with an 8 French suction catheter until clear. Group II received two aliquots of 5 mL/kg of normal saline delivered to the distal tip of the endotracheal tube with an 8 French feeding tube followed by suctioning until clear. Group III received two aliquots of 5 mL/kg of modified natural surfactant extract (Survanta; Ross Laboratories, Columbus, OH) deliv-

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Correspondence: Major Michael S. Paranka, USAF, MC, Department of Pediatrics/SGHP, Wilford Hall USAF Medical Center, Lackland AFB, TX 78236-5300.
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ered to the distal tip of the endotracheal tube with an 8 French feeding tube. Gentle hand bagging was done after each aliquot, followed by suctioning until clear.

The assigned treatment was performed 40 min after meconium administration. Blood gas and ventilatory parameters were performed 20 min after treatment and then hourly for a total of 5 h from meconium instillation.

At 5 h, the piglets were transported to the radiology suite where one chest radiograph was obtained at 1.96 kPa (20 cm H_2O) inflation pressure. Degree of atelectasis was scored on a scale of 1 (none) to 4 (severe) by a pediatric radiologist unaware of treatment group assignment.

At the end of the study, the animals were killed by potassium chloride injection, and a necropsy was performed by veterinary pathology staff unaware of the treatment group assignment. The pathologist was asked to assess gross lung atelectasis on a scale of 1 (normal) to 4 (severe). In addition, histologic specimens were graded for degree of inflammation, edema, and amount of foreign matter.

Approval was obtained from the local animal use committee. All animals were used and cared for in compliance with NIH publication no. 85-23, *Guide for the Care and Use of Laboratory Animals.*

Analyses of variance were used to compare the three treatments at each time period. Specific pairwise comparisons were then made using Tukey methods.

RESULTS

Of the 24 piglets entered, 19 were used for data analysis. Three animals died during meconium instillation, one died of pneumothorax during saline administration, and one died during surfactant treatment. Of the 19 animals successfully managed for 5 h, seven were in group I, five in group II, and seven in group III.

To achieve the goal of a post-meconium a/A ratio < 0.2, some animals required additional doses of 3 mL/kg meconium as noted: group I, two animals required one additional dose, one animal required two additional doses; group II, no animals required additional doses; and group III, one animal required one additional dose, one animal required two additional doses.

The amount of meconium recovered while suctioning group I animals was minimal. Group II animals yielded a return of approximately 2 mL/kg meconium-stained fluid. Approximately 2 mL/kg surfactant/meconium mixture was obtained from group III animals.

Results of a/A ratio are illustrated in Figure 1. All animals had PaO_2 > 53.32 kPa (400 mm Hg) before meconium and all dropped to a PaO_2 < 18.66 kPa (140 mm Hg) within 20 min of meconium administration. For the first 3 h after meconium administration, there was a statistically significant ($p < 0.05$) improvement in the a/A ratio of the surfactant group *versus* both suction and saline.

The pressure required to maintain $PaCO_2$ of 4.67–6.67 kPa (35–50 mm Hg) is reflected in the OI. OI was defined as mean airway pressure × FiO_2 × 100 divided by PaO_2. OI results are shown in Figure 2. The OI was statistically significant ($p < 0.05$) at 1, 3, and 4 h in the surfactant group *versus* the suction only group.

Radiographic and pathologic scores are shown in Figures 3–7. Chest radiographs were available on 15 animals and pathologic analysis was available on all animals except one in group I.

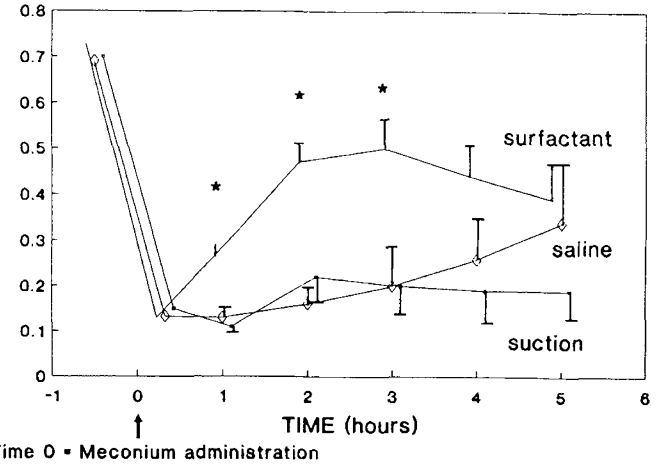

Fig. 1. a/A ratio *vs* time after meconium administration. Mean and SEM are shown for each group at each time point. *, $p < 0.05$ for surfactant *vs* both saline and suction.

DISCUSSION

Delivery room management of the infant with meconium-stained amniotic fluid has been standardized to a combined obstetric and pediatric approach that includes prophylactic suctioning of the oropharynx on the perineum and further tracheal suctioning by the pediatrician as needed. This standard technique may help reduce the mortality associated with MAS, but it has not entirely eliminated the disease (1).

Attempts at mechanical removal of meconium from the infant after MAS have met with limited success (7). Radioisotope-labeled meconium has been shown to move distal to the mainstem bronchi within the first hour of injection and become

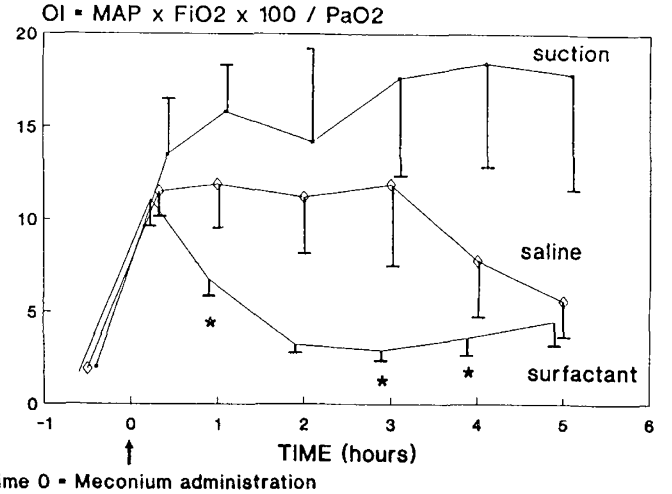

Fig. 2. OI *vs* time after meconium administration. Mean and SEM are shown for each group at each time point. *, $p < 0.05$ for surfactant *vs* suction.

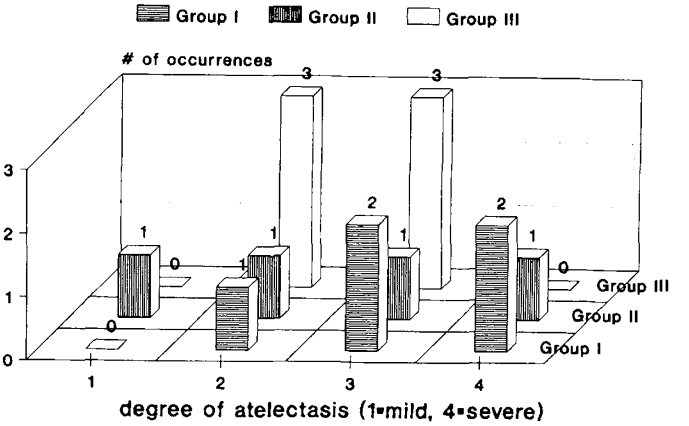

Fig. 3. Chest radiograph scores at the end of the study. Animals were hand ventilated to peak inspiratory pressure of 1.96 kPa (20 cm H_2O).

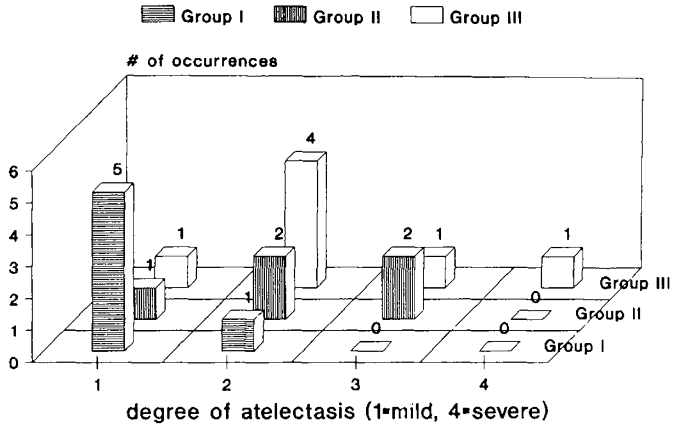

Fig. 4. Gross atelectasis at time of necropsy.

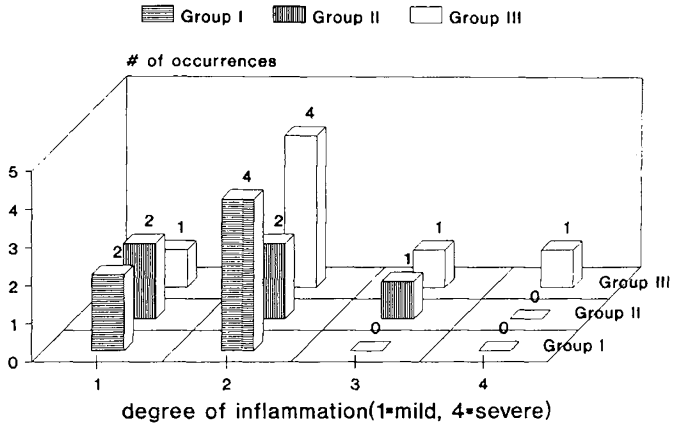

Fig. 5. Degree of inflammation on histologic specimens.

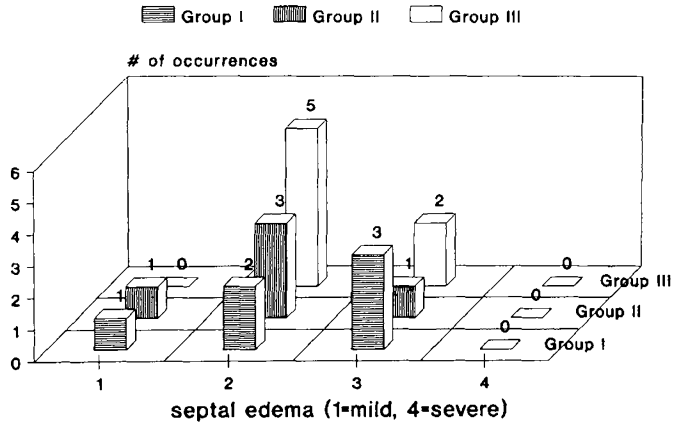

Fig. 6. Degree of septal edema on histologic specimens.

inaccessible to suctioning (8). Saline lavage of infants after MAS has been reported to result in increased respiratory distress (3). The deterioration after saline lavage may be due to removal of significant quantities of surfactant along with the meconium, or the lavage itself may contribute to pulmonary edema and surfactant dysfunction.

Evidence suggests that MAS may be a sequential process of initial large airway obstruction followed by gradual onset of chemical pneumonitis over the next several hours (9). Tran *et al.* (10) demonstrated in a rabbit model of meconium aspiration that the first 120 min were characterized by large and then small airway obstruction without evidence of disruption of surface active proteins. Gooding *et al.* (8) also demonstrated migration of meconium from large airways to the periphery.

The presence of meconium in the distal airways and alveoli

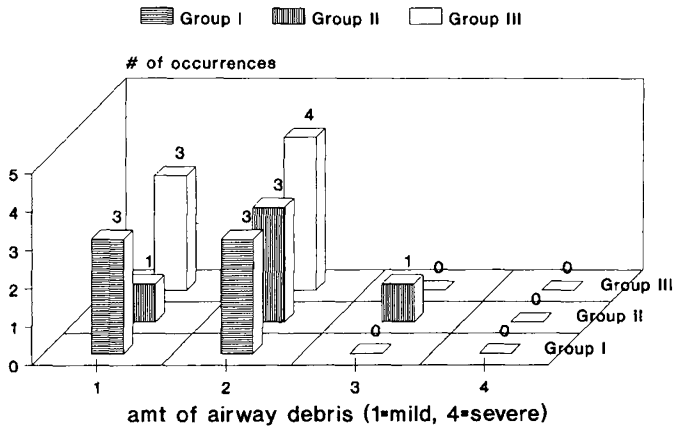

Fig. 7. Amount of foreign material in airways on histologic specimens.

may interfere with surfactant function. The edema and alveolar protein leak produced in MAS may be similar to that of adult respiratory distress syndrome and may also lead to elevation of surface forces by inactivating surfactant.

Clark *et al.* (5) and Chen *et al.* (4) in separate studies demonstrated that the fatty acids present in meconium both *in vivo* and *in vitro* increased surface tension forces. A recent uncontrolled trial (6) of calf lung surfactant extract in 14 term newborns, seven with MAS, resulted in 100% survival and no chronic lung disease. These authors recommend expanded controlled trials.

The results of our study indicate that, in the piglet model of MAS, lavage with exogenous surfactant can produce short-term improvement in oxygenation. Piglets in the surfactant group had a prompt improvement in gas exchange, whereas the suction only group had no improvement during the study period.

As shown in Figures 1 and 2, the saline lavage group had a trend toward improvement in oxygenation over time, although it was a delayed and less significant improvement as compared with the surfactant group. This apparent benefit from saline lavage may represent a clearing of the large airways and so effect a short-term relief from the "obstructive" phase of MAS.

The apparent beneficial effect of saline lavage in this model differs from the finding of Carson *et al.* (3) that saline lavage was not beneficial and may even have a detrimental effect. Their conclusion is based on their saline lavage group having no change in the overall incidence of MAS and on the added morbidity of wet lung disease in five patients. Although the overall incidence of MAS was unchanged, the severity of disease was less in the saline lavage group compared with the group that was neither suctioned nor lavaged. The iatrogenic wet lung disease occurred in five patients who were lavaged despite absence of meconium in the trachea. These results suggest that MAS is best prevented by deep suctioning by obstetricians and pediatricians and that saline lavage performed routinely in meconium-stained infants is potentially harmful.

The improvement in oxygenation with time in our saline lavage group was unexpected, and it suggests that the role for saline lavage in MAS may need to be reconsidered. We speculate that any deterioration in lung function caused by saline lavage might be ameliorated by later use of exogenous surfactant.

The process of administering the surfactant lavage was generally well tolerated by the piglets in this study with the exception of a single death due to pneumothorax. This situation could have been remedied easily with use of a thoracostomy tube, but this was not part of the protocol. The successful use of surfactant lavage in the remaining animals suggests that it can be a safe technique if used carefully with close monitoring of vital signs and early use of chest radiographs as indicated.

The radiographic and pathologic results showed no clear difference among the three groups. Radiographic and pathologic analysis was not done on all the animals; however, the available

data is representative of the three groups. These results may reflect a variable response to the initial meconium administration. The presence of an inflammatory response in the lung parenchyma of all treatment groups after this short-term study suggests the rapid development of a pathologic picture consistent with chemical pneumonitis. Were this disease process allowed to progress, it is possible that these animals would develop a more profound surfactant dysfunction that would benefit from further exogenous surfactant therapy.

In summary, use of surfactant lavage in the piglet model of MAS resulted in significant short-term improvement in oxygenation *versus* control animals. It appears that surfactant lavage can be accomplished safely. A more prolonged animal trial to assess long-term outcome and need for multiple surfactant dosing is warranted. These data demonstrate a clinical benefit of surfactant lavage after acute meconium aspiration and suggest that it may be worthy of future study in human infants with severe MAS.

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Announcements

8th International Steglitz Paediatric Surgical Congress

The 8th International Paediatric Surgical Congress, entitled "Endoscopic Surgery in Children," will be held at the University Medical Centre Steglitz, Berlin, Germany on December 4 and 5, 1992. *For further information, contact* PD. Dr. F. Schier, Kinderchirurgie, Universitätsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Telephone 49 030 798 4181; FAX 49 030 798 4141.

Meeting Announcement

The Society for Behavioral Pediatrics will conduct its 10th Annual Scientific Meeting and Workshops on September 17–21, 1992 at the Hyatt Regency Hotel in St. Louis, MO. *For further information and registration forms, please contact* Ms. Noreen Spota at (215) 248-9168.