Randomized Controlled Trial of Lung Lavage with Dilute Surfactant for Meconium Aspiration Syndrome

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Objective To evaluate whether lung lavage with surfactant changes the duration of mechanical respiratory support or other outcomes in meconium aspiration syndrome (MAS).

Study design We conducted a randomized controlled trial that enrolled ventilated infants with MAS. 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, which in both groups included high frequency ventilation, nitric oxide, and, where available, extracorporeal membrane oxygenation (ECMO).

Results Sixty-six infants were randomized, with one ineligible infant excluded from analysis. Median duration of respiratory support was similar in infants who underwent lavage and control subjects (5.5 versus 6.0 days, $P = .77$). 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). Lavage transiently reduced oxygen saturation without substantial heart rate or blood pressure alterations. Mean airway pressure was more rapidly weaned in the lavage group after randomization.

Conclusion Lung lavage with dilute surfactant does not alter duration of respiratory support, but may reduce mortality, especially in units not offering ECMO. *(J Pediatr 2011;158:383-9)*.

Meconium aspiration syndrome (MAS) is a complex lung disease of the term newborn infant.[1] In the developed world, MAS has become relatively uncommon, with the incidence of MAS requiring intubation being as low as 1 in 2000 live births.[2] In developing and newly industrialized countries, MAS remains problematic,[3,4] in one study accounting for 10% of all cases of neonatal respiratory failure,[3] with a mortality rate of 39%. Therapy for MAS is essentially supportive, with the use of innovative therapies such as high frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) not resulting in a reduction in duration of ventilation or oxygen therapy.[2] Bolus surfactant therapy for MAS has little effect on mortality, risk of pneumothorax, or duration of intubation, but reduces the need for extracorporeal membrane oxygenation (ECMO).[5] Although the use of ECMO has diminished, MAS is still a common antecedent in cases of refractory neonatal hypoxia referred for this therapy.[6] Few centers outside the developed world have the resources to offer ECMO for MAS.[3]

None of the supportive therapies currently applied in MAS interrupt the sequence of pathophysiological disturbances that occur after aspiration of meconium, including airway obstruction,[7,8] alveolar inflammation,[7,9,10] and surfactant inhibition.[11,12] By removing some of the inhaled meconium from the air spaces, therapeutic lung lavage with dilute surfactant may alter the course

$AaDO_2$	Alveolar-arterial oxygen difference
CPAP	Continuous positive airway pressure
ECMO	Extracorporeal membrane oxygenation
HFOV	High frequency oscillatory ventilation
iNO	Inhaled nitric oxide
MAS	Meconium aspiration syndrome
OI	Oxygenation index
P_{AW}	Mean airway pressure

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of disease. Surfactant lavage has shown promise both in experimental models of MAS[13,14] and in ventilated infants with the disease.[15-22] We, and other authors, have found meconium recovery to be optimized with a total lavage fluid volume of 30 mL/kg[14] and an aliquot volume of 15 mL/kg,[14,23] with open suction and chest squeezing.[23,24] This technique was found to be practicable in a preliminary series of ventilated infants with severe MAS.[22]

The aim of this study was to evaluate the efficacy of lung lavage with two 15-mL/kg aliquots of dilute surfactant in ventilated infants with MAS. Our hypothesis was that lavage would shorten the duration of respiratory support, oxygen therapy, and/or hospitalization or may improve other outcomes, including rates of mortality and pneumothorax.

Methods

This was an international multicenter randomized controlled trial of dilute surfactant lavage in MAS, approved by institutional ethical review committees, national ethical review committees, or both. Participating centers (n = 20) were tertiary level neonatal intensive care units, each equipped with standard therapeutic modalities for MAS, including HFOV and iNO. Half the participating centers had access to ECMO. A training workshop was conducted at each center, including a simulation of lavage at the bedside with a resuscitation mannequin. An independent data monitoring and safety committee reviewed the data after the enrollment of 10, 33, and 66 infants. The trial extended from March 2003 until September 2008.

All infants ventilated with MAS in each center were screened for eligibility. The diagnosis of MAS required evidence of passage of meconium at or before delivery, respiratory distress within 2 hours of birth, and typical chest radiographic appearance. Infants with MAS were eligible when they were ≥36 weeks gestation and 2.0 kg birth weight, <24 hours of age, and mechanically ventilated with a mean airway pressure (P_{AW}) ≥12 cm H_2O and on two sequential blood gases had an alveolar-arterial oxygen difference ($AaDO_2$ [$AaDO_2 = FiO_2 \times 713 - PaCO_2/0.8 - PaO_2$]) of at least 450 mm Hg. Subsequent improvement in oxygenation was allowable as long as FiO_2 remained >0.5 before randomization. Infants were excluded from randomization when withdrawal of active treatment was being considered, there was structural cardiac disease, or there was cardiorespiratory instability incompatible with performing lavage (pH <7.20, preductal SpO_2 <85%, and/or mean blood pressure <35 mm Hg). Parents gave written informed consent before randomization.

Infants were assigned to receive either lung lavage or no lavage (control subjects) in a 1:1 ratio in randomly permuted blocks of 2 or 4, stratified by study center. Randomization was performed by a statistician, who prepared sequentially numbered sealed opaque envelopes held at each center.

Study Intervention

Infants randomized to lung lavage received this therapy once all necessary measures had been performed to optimize their condition. The lavage technique is demonstrated in an accompanying **Video** (available at www.jpeds.com) (**Figure 1**; available at www.jpeds.com). All infants were sedated, and administration of muscle relaxants was strongly recommended. Lung lavage was performed by an experienced neonatologist trained in the technique, along with several assistants. Blinding of the intervention from the treating clinicians was not possible.

The lavage fluid was a 1 in 5 dilution of bovine surfactant (Survanta, Abbott Australasia, Kurnell, Australia) in normal saline (final concentration, 5 mg/mL). Two aliquots of 15 mL/kg were administered, with an intervening recovery period until SpO_2 was >80%. Lavage fluid was instilled over 20 seconds through a dispensing catheter placed 0.5 cm beyond the endotracheal tube tip with the ventilator circuit disconnected. Three positive pressure inflations (peak pressure as high as 30 cm H_2O) were then administered with a standard resuscitation bag or ventilator, and the ventilator circuit was once again disconnected to allow recovery by suction of as much of the instilled fluid as possible with a standard suction catheter and –150 mm Hg suction pressure. All aspirated fluid was collected into a suction trap, and its volume and appearance were recorded.

After lavage, infants were returned to their earlier mode of ventilation, and efforts were made to restore lung volume and clear residual lavage fluid by using increased peak pressure, end-expiratory pressure, or both on conventional ventilation or increased P_{AW} on HFOV. Chest radiography was performed within 4 hours to exclude new air leak.

In both groups, ventilatory management and the use of HFOV, iNO, and bolus surfactant therapy were at the discretion of the treating clinicians. Predefined criteria were used for extubation and cessation of nasal continuous positive airway pressure (CPAP) extubation: FiO_2 ≤0.4; end-expiratory pressure, ≤6 cm H_2O (or P_{AW} ≤10 cm H_2O on HFOV); ventilator rate, ≤20 per minute (or inflating pressure, ≤10 cm H_2O), arterial pH ≥7.25; cessation of CPAP: FiO_2 ≤0.4; CPAP, ≤6 cm H_2O; and arterial pH ≥7.25. Referral for ECMO was at the discretion of the clinical team, with accepted severity criteria, including oxygenation index (OI [$OI = (P_{AW} \times FiO_2 \times 100)/PaO_2$]) >40, used to identify infants at high risk of mortality.[6]

Outcomes

The primary outcome measure was duration of respiratory support, defined as the cumulative duration of all periods of intubation and nasal CPAP. Secondary outcomes included death, pneumothorax, and duration of intubation, oxygen therapy, HFOV, iNO, and hospitalization.

Evaluation of the physiological effects and safety of lavage was performed using data on heart rate, mean blood pressure, SpO_2, and blood gas analyses. Longitudinal changes in P_{AW}, $AaDO_2$, and OI were recorded in the first 72 hours