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

after randomization. Several longer-term outcomes have been specified, including neurological and developmental outcome at 2 years. These results will be reported separately.

Statistical Analysis

Australian and New Zealand Neonatal Network data indicate that for the years 1995-2000, infants with severe MAS receiving HFOV, iNO or bolus surfactant had a duration of respiratory support of 6.5 days (geometric mean, lognormally distributed) with an SD of 5.6.[2] A 30% reduction in duration of respiratory support was deemed to be of clinical importance, meaning approximately 2 days less ventilation for each infant with MAS. Detection of an effect of this magnitude with a two-tailed P value <.05 and a power of 80% required randomization of 66 infants.[25]

OR with 95% CI on the basis of Woolf's approximation and Fisher exact tests were used to compare proportions in the two groups for the main dichotomous outcomes. The primary endpoint comparison, duration of respiratory support, is reported as a geometric mean ratio with 95% CI, with corresponding t test in the log scale. For simplicity, this and other continuous outcomes (all right-skewed) were also summarized with medians and inter-quartile ranges, with evidence for differences between groups assessed with the Mann-Whitney test. Longitudinal physiological data and ventilation indices were compared in groups by using linear mixed models. All reported P values are two-tailed.

Results

The numbers of infants screened, eligible for inclusion, excluded, and randomized are shown in Figure 2. Of 328 infants ventilated with MAS during the study period, 118 (36%) met inclusion criteria, with 12 excluded on the basis of cardiorespiratory instability (Figure 2). The 66 infants were enrolled from 13 participating centers (Appendix). Demographic and clinical characteristics of the two groups were similar at the time of randomization (Table I). All infants were from singleton pregnancies. Meconium-staining of the amniotic fluid was noted to be "thick," except in two infants in the lavage group and one infant in the control group. Oropharyngeal suction (either intrapartum or during delivery room resuscitation and stabilization) was performed in 93% of infants who underwent lavage and 97% of the control subjects.

The duration of respiratory support did not differ between the groups, either with all infants included (geometric mean ratio, 0.95; 95% CI, 0.65-1.40; P = .79) or considering only infants who survived (Table II). There were 11 deaths, with one death in each group caused by hypoxic-ischemic encephalopathy and all other deaths caused by hypoxic respiratory failure. The mortality rate was 10% (3/30) and 23% (8/35) in the lavage and control groups, respectively (OR, 0.38; 95% CI, 0.090-1.600; P = .20). Three control infants received ECMO, at 14, 47, and 101 hours of age. Post hoc analysis showed evidence for a difference in the composite outcome of death or requirement for ECMO (10% [3 of 30] versus 31% [11 of 35]; OR, 0.24; 95% CI, 0.060-0.970; Fisher exact two-sided P = .067), implying that proportionally more infants receiving lavage survived without ECMO. The mortality rate at the 6 centers offering ECMO was 18% (2/11) in infants receiving lavage, compared with 14% (2/14) in control subjects (OR, 1.3; 95% CI, 0.16-11.00; P = 1.0), with one death in each group caused by hypoxic-ischaemic encephalopathy. An additional 3 control infants with profound hypoxia were treated with ECMO, and each of them survived. At the 7 centers not offering ECMO, the mortality rate was 5.3% (1/19) in infants received lavage and 29% (6/21) in control subjects (OR, 0.14; 95% CI, 0.015-1.300; P = .095).

The duration of intubation, oxygen therapy, hospitalization, HFOV, and iNO were similar in the two groups. Two infants who underwent lavage and 4 control subjects received oxygen at home. Rates of pneumothorax were similar in groups; pneumothorax developed after randomization in 1 infant who underwent lavage and 5 control subjects (3.3% versus 14%; OR, 0.21; 95% CI, 0.023-1.900). Of these 6 infants, only one (control group) survived. Bolus surfactant therapy (100 mg/kg) was given to two infants who underwent lavage and 4 control subjects after randomization. Inclusion in the lavage group of the ineligible infant who was randomized but not lavaged (ie, intention-to-treat analysis) did not substantially affect the results in relation to primary and secondary outcomes (Table III; available at www.jpeds.com), but weakened the OR in relation to survival without ECMO (OR, 0.32; 95% CI, 0.091-1.200).

Pulmonary hypertension was noted in 17 of 22 infants in the lavage group in whom an echocardiogram was performed (77%), and 18 of 23 control subjects (78%). Pulmonary hemorrhage occurred in 3 infants in the lavage group (1 pre-lavage, 2 others >40 hours post-lavage), and in 1 control subject 5 hours after randomization.

Infants randomized to lavage received this treatment at 14.0 ± 5.9 hours of age (mean ± standard deviation), with the maximum age being 24.8 hours. Lavage was done within 4 hours of randomization in all infants except one, in whom the procedure was delayed for 10 hours until cardiorespiratory status was satisfactory. In one case in which Survanta was unavailable, poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) was used; exclusion of this infant from the analysis did not significantly alter the findings. Both lavage aliquots were administered to all infants, with 9.0 ± 7.3 minutes between aliquots (maximum, 37 minutes) and a total duration of the procedure of 14.0 ± 9.2 minutes (maximum, 48 minutes).

Lavage return volume for the first, second, and combined aliquots was 39% ± 15%, 52% ± 18%, and 46% ± 14% of the instilled volume, respectively. Lavage fluid was reported to be blood-stained in 26 cases (87%), and was visibly meconium-stained (without centrifugation) in 14 cases (47%). Coughing or gagging occurred in two infants, neither of whom was muscle-relaxed. Two infants had a heart rate transiently

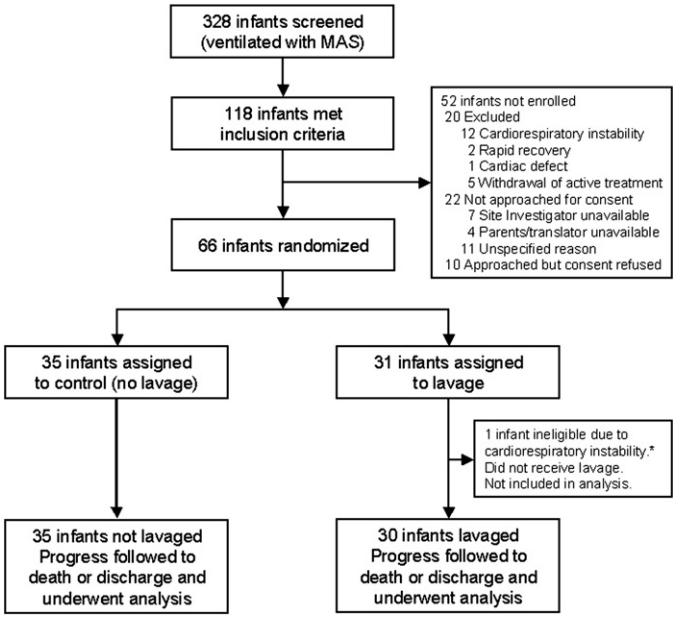

Figure 2. Enrollment and randomization. *Infant 20-01 was found to have been ineligible for randomization because of cardiorespiratory instability, with an arterial pH of 6.9 before and after randomization. The infant was randomized to the lavage group, but did not receive lavage, and died at 11 hours after randomization. All other infants had an arterial pH > 7.20 at the time of randomization.

<100 beats per minute during lavage, with recovery to >150 beats per minute by 5 minutes post-lavage. One of these infants died at 3 hours post-lavage with severe pulmonary hypertension. This infant had a pre-lavage PaO_2 of 24 mm Hg despite HFOV and inhaled nitric oxide and a total lavage return volume of 10%.

In the lavage group overall, cardiorespiratory indices were only transiently affected by the procedure and recovered rapidly to approximate near pre-lavage values within 5 minutes (**Figure 3**; available at www.jpeds.com). SpO_2 fell during lavage, and in 5 infants it remained <80% for >10 minutes. Other than the infant with intractable pulmonary hypertension, SpO_2 was >90% in all cases by 40 minutes. Change in mean blood pressure was not significant in most cases; 6 infants required treatment for hypotension during or immediately after lavage (increasing inotrope dosage in 4 infants, and a fluid bolus in 2 infants).

At 4 hours post-lavage, infants in the lavage group had similar blood gas indices to infants in the control group (**Figure 4**; available at www.jpeds.com). No new pneumothoraces were noted on post-lavage chest radiography. Compared with control subjects, infants receiving lung lavage had a greater reduction in P_{AW} in the first 24 hours after randomization ($P = .005$; **Figure 5**).

Discussion

MAS is a serious newborn respiratory disorder for which there is a frustrating lack of specific therapy.[1] In this study, we examined the impact of lung lavage in MAS, with a technique developed in a series of laboratory experiments[14] and evaluated in a preliminary study in ventilated infants.[22] We found no evidence for an effect of lavage on duration of respiratory support, but there appeared to be a reduction in mortality, especially when infants ostensibly saved with ECMO were considered with infants who died.

Previous evaluation of dilute surfactant lavage in infants with MAS has been limited to cohort studies[16,17,19-22] and two small randomized controlled trials enrolling 32 infants.[15,18] Pooled data from these reports suggest a potential benefit of lavage, in particular reductions in duration of

Table I. Demographic and clinical characteristics of the randomization groups

Characteristic	Lavage (n = 30)	Control (n = 35)
Male	19 (63%)	17 (49%)
Gestation (wk)	39 (38-40)	40 (39-41)
Birth weight (kg)	3.4 (3.0-3.6)	3.5 (3.2-3.9)
Inborn	17 (57%)	23 (66%)
Caesarean delivery	21 (70%)	25 (71%)
Apgar score at 5 minutes	7 (6-8)	7 (5-8)
Intubated in delivery room	16 (53%)	20 (57%)
Age (hours) at randomization (mean ± SD)	13.0 ± 5.9	12.0 ± 6.3
HFOV before randomization	18 (60%)	23 (66%)
iNO before randomization	16 (52%)	16 (47%)
Bolus surfactant before randomization	3 (10%)	3 (8.6%)
Inotrope infusion before randomization	23 (77%)	28 (80%)
$AaDO_2$ (mm Hg) at randomization (mean ± SD)	490 ± 130	520 ± 100

SD, standard deviation. All continuous variables expressed as median (interquartile range) unless stated; dichotomous variables expressed as n (%).

ventilation and risk of pneumothorax.[26] Despite small subject numbers, 3 of these studies reported a reduction in duration of ventilation in infants treated with lavage compared with historical control subjects.[16,20,21]

Several factors may have contributed to the lack of effect of lung lavage on duration of respiratory support in our study, beyond the potential role of chance. The time required for confirmation of eligibility and obtaining consent meant that lavage was performed relatively late, on average 14 hours after birth. Aspiration of meconium would appear to be largely a prenatal event, with clearance of meconium from the airways postnatally having no effect on the development of MAS in meconium-stained infants.[27] After inhalation, meconium undergoes gradual distal migration,[7,8] causing bronchiolar obstruction and inducing an inflammatory reaction that peaks between 12 and 24 hours.[7,9,10] A long delay in performing lavage after birth therefore will inevitably limit its potential effectiveness.

The lack of effect of lavage on duration of respiratory support may also relate to the severity of cardiopulmonary disease in the enrolled infants. The study group had a high rate of coexistent pulmonary hypertension and systemic hypotension requiring inotrope therapy, conditions that may retard weaning from respiratory support. Infants with predominantly parenchymal lung disease may have been underrepresented. An earlier randomized controlled trial of lavage therapy targeted such infants, with the lavage group having a mean OI at enrollment of 12 (versus 25 in our study).[18] Compared with the duration of ventilation in control subjects, a trend toward reduction in duration of ventilation was noted after lavage.

There did appear to be an effect of lung lavage on survival without ECMO. The composite outcome of death or requirement for ECMO, although not pre-specified, took in account that the risk of mortality at each center was potentially influenced by the availability of ECMO. Whereas in study centers not offering ECMO there was substantially higher mortality rate in control subjects (albeit with considerable statistical uncertainty because of the small numbers), in ECMO centers the mortality risk was similar in the two arms, with 3 control subjects surviving after treatment with ECMO. These infants were profoundly hypoxic before being cannulated for ECMO and may well have died had they not received this therapy. ECMO is largely unavailable outside the developed world,[3] and we contend that for centers offering a high level of supportive respiratory care but not ECMO, lung lavage may reduce mortality in infants with severe MAS.

Table II. Main outcomes

Outcome	Lavage (n = 30)	Control (n = 35)	*P* value*
Days on respiratory support	5.5 (3.4-12)	6.0 (4.3-10)	.77
Days on respiratory support (survivors)	8.0 (4-13)	7.8 (4.7-10)	.86
Died	3 (10%)	8 (23%)	.20
Received ECMO	0 (0%)	3 (9%)	.24
Died or received ECMO	3 (10%)	11 (31%)	.067
Days of intubation (survivors)	5.0 (3.3-8.7)	6.3 (3.9-8.1)	.57
Days of oxygen therapy (survivors)	14 (6.7-21)	14 (11-18)	.48
Days in any hospital	16 (9.7-23)	18 (10-24)	.70
Days in any hospital (survivors)	17 (11-25)	19 (15-25)	.46
Days of HFOV (survivors)	2.1 (0-5.3)	3.9 (0.8-6.0)	.34
Days of iNO therapy (survivors)	2.9 (0-4.0)	2 (0-6.0)	.70
Pneumothorax	7 (23%)	8 (23%)	1.0
Pneumothorax after randomization	1 (3.3%)	5 (14%)	.21

All continuous variables expressed as median (interquartile range); dichotomous variables expressed as n (%).
**P* values from Mann-Whitney test (continuous outcomes) and Fisher exact test (dichotomous outcomes).

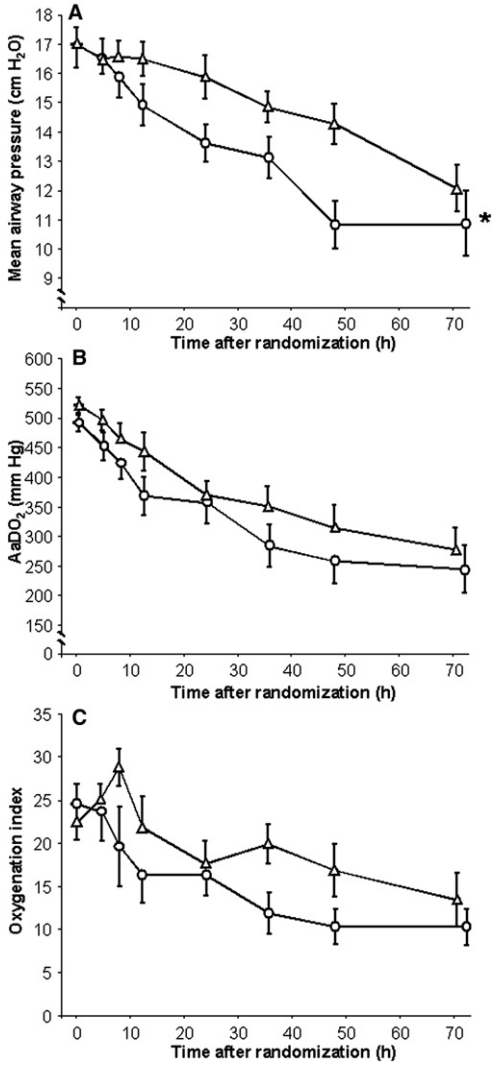

Figure 5. Ventilation indices in the first 72 hours after randomization. **A,** P_{AW}, **B,** $AaDO_2$, and **C,** OI at and for the first 72 hours after randomization. Mean and SEM. *Circles* represent infants who underwent lavage; *triangles* represent control subjects. One infant who underwent lavage and two control subjects died during this period; data from these infants are plotted until death. Data are incomplete for a further 3 infants (2 who underwent lavage) because of missing arterial blood gas results. Two control infants went onto ECMO at 6.5 and 30 hours after randomization; thereafter, values for each variable are assumed to lie on a trajectory between the last pre-ECMO and first post-ECMO reading. *P_{AW} was lower in the lavage group during the first 24 hours.

In consideration of how survival might be improved by lavage, it is noteworthy that lavaged infants in our study had lower P_{AW} in the first 24 hours after randomization, as reported previously.[16,21] The resultant potential reduction in barotrauma may have helped to prevent ventilator-induced lung injury. Minimization of barotrauma is an important principle of management in MAS, because of the relatively high risk of pneumothorax and the higher mortality rate associated with this complication.[28]

Lung lavage with dilute surfactant in MAS may also facilitate the homogeneous distribution of surfactant to the distal air spaces.[29] With conventional bolus dosing, surfactant is known to distribute unevenly within the lung,[30] a likely contributor to the limited impact of bolus surfactant therapy noted in randomized controlled trials.[5] Early trials of bolus surfactant therapy in MAS with large cumulative doses of surfactant showed a reduction in the risk of EMCO in infants treated with surfactant.[31,32] Two more recent trials, conducted in centers not offering ECMO, showed no benefit of bolus surfactant on any significant outcome, including mortality, air leak, or duration of ventilation.[33,34] For this reason, we elected not to mandate bolus surfactant therapy in the control arm of our study of lavage therapy in MAS. This may be a limiting factor in the interpretation of our results in centers in which bolus surfactant therapy is used routinely in MAS.

Notwithstanding the high incidence of pulmonary hypertension and the potential for its exacerbation by lavage,[35] the group of infants who underwent lavage in our study were not destabilized for a prolonged period by the procedure. Both aliquots of lavage were administered in all infants, in most instances with minimal disturbance of heart rate and blood pressure. As predicted, and as previously noted,[18,22] SpO_2 fell to low levels during and after lavage, with recovery in most cases to 80% within 10 minutes and to 90% within 40 minutes. One infant died with intractable pulmonary hypertension 3 hours after lavage, and a worsening of the condition may have been precipitated by the procedure. The lavage return volume (only 10% of the instilled volume) suggests suctioning was incomplete in this case, and thus pulmonary flooding may have contributed to the ongoing hypoxia.

Several limitations of our study are evident. The intervention was not blinded from the clinical team, raising the possibility that choice of treatments after randomization (including HFOV, iNO, or ECMO) was biased by knowledge of the allocation group. The study was conducted in centers both with and without access to ECMO, and for this reason the need for ECMO was not a pre-specified outcome, nor were formal criteria placed around its use. Finally, the slow rate of recruitment meant that experience with lung lavage in each participating center was limited, which may have had an impact on the effectiveness of the therapy.

Our study demonstrated that dilute surfactant lavage is achievable in ventilated infants with severe MAS and a high risk of mortality. The uncertainties related to the relatively small number of recruits and post hoc statistical analysis preclude a definitive recommendation to adopt lavage therapy in such infants. We would encourage centers with a high MAS incidence and mortality rates to participate in further clinical trials of this therapy.

In conclusion, lung lavage with two 15 mL/kg aliquots of dilute surfactant in ventilated infants with severe MAS does not appear to substantially alter duration of respiratory support, but may produce a reduction in mortality, especially in units not offering ECMO. A further clinical trial enrolling a larger number of infants would help to more precisely define the effect on survival. ■

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Appendix

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Table III. Main outcomes (intention-to-treat analysis)*

Outcome	Lavage (n = 31)	Control (n = 35)	*P* value†
Days on respiratory support	5.4 (3.2-12)	6.0 (4.3-10)	.77
Days on respiratory support (survivors)	8.0 (4-13)	7.8 (4.7-10)	.86
Died	4 (13%)	8 (23%)	.30
Received ECMO	0 (0%)	3 (9%)	.24
Died or received ECMO	4 (13%)	11 (31%)	.086
Days of intubation (survivors)	5.0 (3.3-8.7)	6.3 (3.9-8.1)	.57
Days of oxygen therapy (survivors)	14 (6.7-21)	14 (11-18)	.48
Days in any hospital	15 (9.3-23)	18 (10-24)	.70
Days in any hospital (survivors)	17 (11-25)	19 (15-25)	.46
Days of HFOV (survivors)	2.1 (0-5.3)	3.9 (0.8-6.0)	.34
Days of iNO therapy (survivors)	2.9 (0-4.0)	2 (0-6.0)	.70
Pneumothorax	7 (23%)	8 (23%)	1.0
Pneumothorax after randomization	1 (3.2%)	5 (14%)	.20

All continuous variables expressed as median (interquartile range); dichotomous variables expressed as n (%).

*Infant 20-01, found to be ineligible because of cardiorespiratory instability, is included in the lavage group (ie, intention-to-treat analysis). This infant was too unstable to receive lavage and died 11 hours after randomization.

†*P* values from Mann-Whitney test (continuous outcomes) and Fisher exact test (dichotomous outcomes).

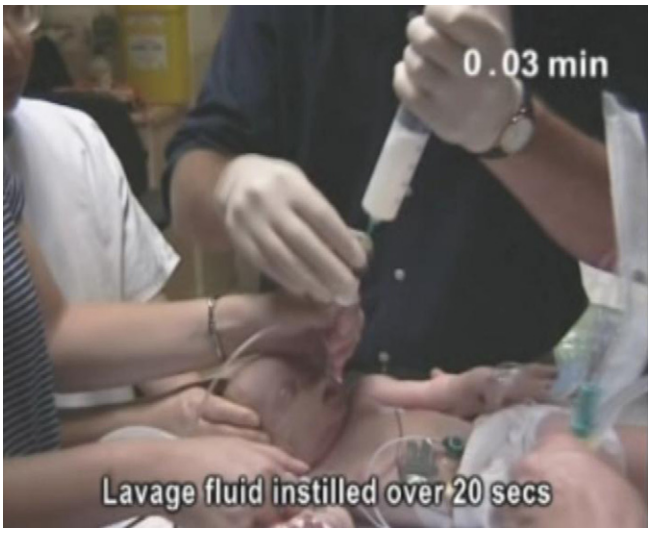

Figure 1. Beginning of instillation of the first lavage aliquot.

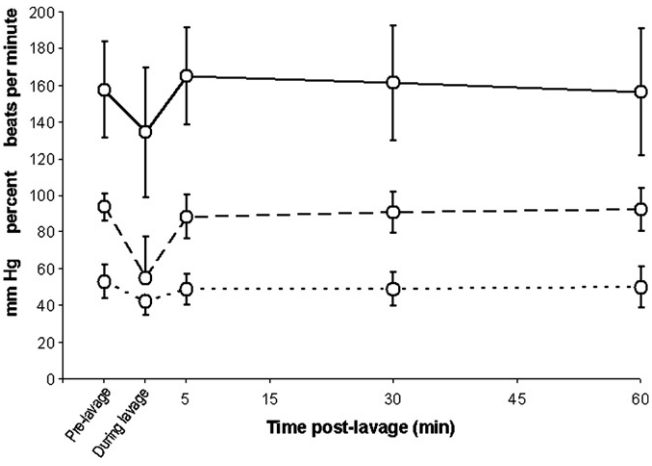

Figure 3. Cardiorespiratory indices before, during, and after lavage. Heart rate (*solid line*; Y-axis units: beats per minute), SpO_2 (*dashed line*; units: %), and mean blood pressure (*dotted line*; units: mm Hg) before lavage, minimum values noted during lavage, and post-lavage. Mean and SD.

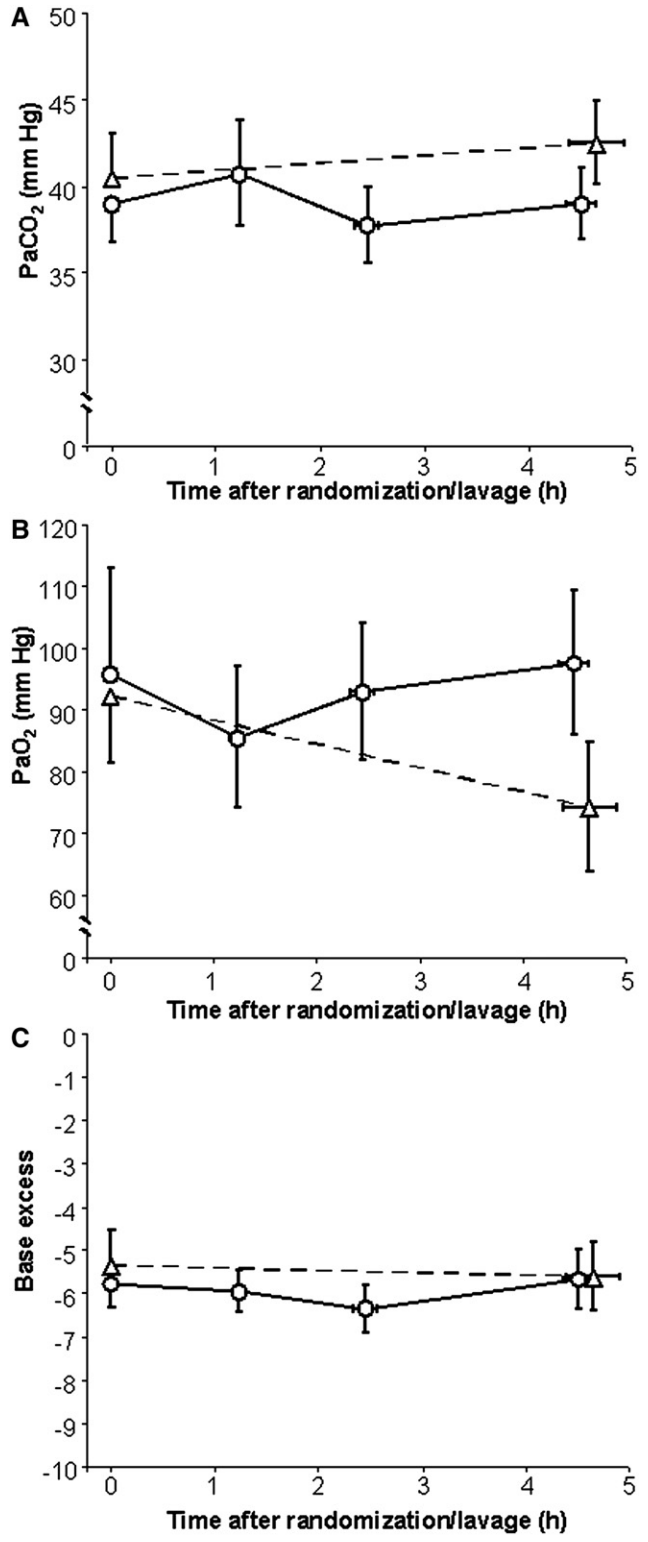

Figure 4. Arterial blood gas variables before and after lavage. **A,** $PaCO_2$, **B,** PaO_2, **C,** Base excess before and for the first 4 hours after lavage. Mean and SEM. *Circles* represent infants who underwent lavage; *triangles* represent control subjects (values at randomization and 4 hours after randomization). No significant differences are noted in the two groups at 4 hours.