

## Surfactant Lung Lavage versus Standard Treatment for Meconium Aspiration Syndrome

TAREK K. ALSAYAD, M.D.; EHAB I. SOROUR, M.D.; MOHAMED MOUSTAFA, M.D. and ASHRAF ABDELKADER, M.D.

*The Department of Pediatrics, Faculty of Medicine, Al Azhar University*

### Abstract

**Background:** To evaluate diluted surfactant lung lavage as a therapy for severe meconium aspiration syndrome.

**Aim of Study:** The aim of this study is to evaluate the efficacy and outcome of lung lavage using diluted surfactant compared to standard protocol for treatment of meconium aspiration syndrome.

**Patients and Methods:** This was a prospective interventional study involved 24 patients with severe meconium aspiration syndrome divided into two equal groups one received the standard care in the form of high frequency ventilation and the second group received pulmonary lavage using diluted surfactant in addition to the standard care. Pulmonary lavage was done using of 15ml/kg of surfactant diluted to concentration of 5mg of phospholipids/1ml of 0.9% NaCl divided into four equal aliquots.

**Results:** On comparing both groups patients managed by pulmonary lavage using diluted surfactant showed significant improvement in PCO<sub>2</sub> and mean airway pressure occurred 6 hours after lavage while improvement in PO<sub>2</sub>, oxygenation index and arterial-alveolar oxygen gradient occurred 24 hours after lavage. The duration of mechanical ventilation, oxygen therapy and hospital stay were shorter in the surfactant group. There was no difference between both groups in the incidence of complications, need for ECMO or death.

**Conclusion:** Surfactant lung lavage is a safe and effective therapy for severe meconium aspiration syndrome.

**Key Words:** Meconium – Aspiration – Surfactant – Lavage – Neonates.

### Introduction

**MECONIUM** aspiration syndrome (MAS) is a common cause of respiratory failure in full term newborns. MAS constitute more than 50% of indications of mechanical ventilation in babies born after 39 weeks [1]. Moreover, MAS is the primary diagnosis for a significant proportion of those

newborns requiring extracorporeal membrane oxygenation (ECMO) in the United States (26%) and the United Kingdom (51 %). In the developed world, MAS incidence decreased as low as 1 in 2000 live births. In the developing countries, MAS remains problematic [2].

Intrauterine fetal hypoxia leads to relaxation of sphincters and stimulation of colonic movements with passage of meconium into amniotic fluid. Also, hypoxia itself stimulates gasping intrauterine or during the first few breaths after delivery. The end result is aspiration of meconium into airways [3,4].

Pathophysiology of MAS is complex and includes airways obstruction, meconium induced chemical pneumonitis with release of inflammatory mediators, surfactant dysfunction and persistent pulmonary hypertension. These factors lead to hypoxemia and decreased lung compliance. Poor oxygenation is attributed to a combination of ventilation perfusion mismatching, intrapulmonary shunting due to regional atelectasis and extrapulmonary shunting due to persistent pulmonary hypertension [5].

Meconium impairs lung surfactant by different mechanisms: (a) Displaces surfactant from alveolar spaces, (b) Affects surfactant function by a combined action of its cholesterol and bile acids, (c) Has direct toxicity on type II pneumocytes, and (d) Decreases surfactant proteins A and B [6].

Meconium also has a detrimental effect on placental and umbilical tissues, resulting in vasoconstriction, ulceration, and vascular necrosis, potentially compromising fetal oxygenation. It inhibits fetal lung fluid reabsorption at birth through unknown mechanisms, disturbing the ability of the

**Correspondence to:** Dr. Tarek K. Alsayad, The Department of Pediatrics, Faculty of Medicine, Al Azhar University

lungs to adapt properly to extrauterine life. Further detailed studies to elucidate the changing concepts in pathophysiology of MAS from mechanical obstruction to the role of immuno-inflammatory mechanisms are required for exploring newer strategies in the management of MAS [7].

Initial therapy for meconium aspiration is supportive aiming to clear meconium through suctioning of upper airways immediately after delivery and tracheal toileting in case meconium-stained newborns soon after delivery if the baby is not vigorous [7,8]. When needed, neonate is admitted to intensive care unit (NICU) to maintain adequate oxygenation and optimal blood pressure, correct acidosis, and other metabolic disorders. Supplemental oxygen administration in many less severe cases is the only therapy [9].

About one third of those infants require intubation and mechanical ventilation due to worsening respiratory status. The use of mechanical ventilation carries the hazards of increased risk of barotrauma due to the complicated pulmonary pathophysiology involving areas of atelectasis and areas of hyperinflation, in association with ventilation-perfusion mismatch and airway obstruction. High frequency oscillatory ventilation (HFOV) is now an important means of providing respiratory support for infants with severe MAS failing conventional ventilation [10].

All previous lines of treatment are supportive, but they do not hinder the pathogenesis. Removal of meconium using saline bronchoalveolar lavage was tried with reasonably accepted results, but it has drawbacks of increasing the amount of liquid in the lungs, dilute endogenous surfactant, and cause its partial removal together with the lavage fluid. So, when saline lung lavage is used, substitution of surfactant is recommended [11].

Intra-tracheal bolus of undiluted surfactant as a treatment for MAS was first tried in animals with experimentally induced MAS and showed improvement in pulmonary function. Similar results were observed also in newborns with MAS [12].

Several doses of undiluted surfactant may be required to give adequate results and earlier surfactant administration is associated with better results [2]. Rapid changes in pulmonary vascular resistance and subsequent hemodynamic changes associated with large bolus of surfactant can lead to increased risk of intraventricular hemorrhage. So, when using undiluted surfactant bolus it is better to be divided into several small portions and

delivered as a slow tracheal infusion to prevent acute hemodynamic changes [13].

Early pulmonary lavage with diluted surfactant solution was first tried in animals with significant improvement in respiratory function while using smaller amount of surfactant and carrying less drawbacks. Application of this method in neonates with MAS showed good results [14].

For the lung lavage, exogenous surfactant is usually diluted to a concentration of 5mg of phospholipids/ml, which is sufficiently resistant to inactivation by meconium and plasma proteins [2,15].

### Patients and Methods

This is a prospective interventional study was carried out at United Doctors Hospital, Jeddah, KSA, over the period from January 2014 till March 2015 and included 24 patients divided into two groups each one was 12 patients. Both groups were diagnosed as meconium aspiration syndrome and fulfilled our inclusion criteria. One group (control group) received the standard care in the form of high frequency ventilation and the second group (intervention group) was additionally managed by pulmonary lavage using diluted surfactant. Both groups received the standard respiratory care.

#### *Inclusion criteria:*

Full term newborn requiring mechanical ventilation during the first 6 hours of life due to meconium aspiration syndrome. Indications of mechanical ventilation were fraction of inspired oxygen (FiO<sub>2</sub>) requirement >0.4, arterial partial pressure of oxygen (PaO<sub>2</sub>) <50mmHg and arterial partial pressure of carbon dioxide (PCO<sub>2</sub>) >60mmHg. We included infants with significant respiratory compromise confirmed by two repeated blood gases showing alveolar-arterial oxygen difference of at least 450mm Hg.

- Gestation age  $\geq$  36 week and birth weight  $\geq$  2.5kg.
- Evidence of meconium aspiration syndrome.
- Presence of meconium-stained amniotic fluid or staining of meconium in skin, umbilical cord or nails.
- Presence of meconium below vocal cords.
- Non-vigorous babies.
- Chest X-ray suggestive of meconium aspiration.
- Presence of respiratory distress (Downe's score  $\geq$  4) within 2 hours of birth.
- Need for mechanical ventilation within 6h of birth.

*Exclusion criteria:*

- Major congenital malformations.
- Congenital heart disease.
- Hydrops fetalis.
- Air leaks, before Surfactant Lung lavage.
- Pulmonary hemorrhage, before Surfactant Lung lavage.
- Infants in whom transfer to other hospital is likely.

*Primary outcome:*

- Change in respiratory indices: Oxygenation index (OI), alveolar-arterial Oxygen gradient (A-a gradient), and mean airway pressure (MAP). These values were measured from before and 1, 6, 24h and 48 hours following treatment.
- The duration of mechanical ventilation, oxygen therapy and hospital stay were determined.

*Secondary outcome:*

- Complications: Incidence of pulmonary hypertension by Echocardiography and pneumothorax by chest X-ray, intracranial hemorrhage confirmed by cranial ultrasound.
- Incidence of sepsis: Confirmed sepsis defined as sepsis Screen positive + Blood or CSF culture positive for bacteria.

*Sepsis screen:*

- Total leukocyte count  $<5000/\text{mm}^3$ .
- Absolute neutrophil count  $<1500/\text{cu. mm}$ .
- Immature/total neutrophil ratio  $>0.2$ .
- Micro-ESR  $>15\text{mm}$  in <sup>1st</sup> hour.
- C Reactive Protein (CRP)  $>10\text{mg/dl}$ .

*Surfactant lung lavage:*

Surfactant lung lavage was performed on the study group of newborns during the first 6 hours of life. The natural surfactant (Survanta; Abbott Laboratories, Abbott Park, IL, USA) was diluted to concentration of 5mg of phospholipids/1ml of 0.9% NaCl. The diluted surfactant was given in a dose of 15ml of solution per kg of body weight divided into four equal aliquots. Lavage fluid was instilled through a catheter placed 0.5cm beyond

the endotracheal tube. This was followed by positive pressure inflations (peak pressure as high as 30cm H<sub>2</sub>O) using a suitable self-inflating bag. After each surfactant aliquot had been obtained, standard suction system was used to recover as much of the instilled fluid as possible.

*Statistical analysis of data:*

Statistical analysis was carried out using the SPSS computer package version 19.0 (SPSS Inc., Chicago, IL, USA). The collected data were statistically managed as follows:

- For descriptive statistics: The mean  $\pm$  SD were used for quantitative variables while the number and percentage were used for qualitative variables.
- For analytic statistics: Qualitative variables were compared by Fischer's exact test (FET), and quantitative variables were compared by independent samples *t*-test.
- The statistical methods were verified, assuming a significant level of  $p < 0.05$  and a highly significant level of  $p < 0.001$ .

**Results**

This study involved 24 patients with significant respiratory distress due to MAS, 12 patients of them received the standard care including high frequency mechanical ventilation and the other 12 patients were additionally managed by bronchoalveolar lavage using diluted surfactant. There was no significant difference regarding general characteristics of the included newborns as shown in (Table 1). The time of doing bronchoalveolar lavage was  $4 \pm 2.9$  (1.1-6.9) hours after delivery. (Tables 2,3) show results of respiratory indices for the studied newborns which were measured before intervention and repeated 1, 3, 6, 24 and 48 hours after doing surfactant lavage. The first parameters showed significant difference were PCO<sub>2</sub> and MAP which were lower to normal in surfactant group 6 hours after doing surfactant lavage. Also, PO<sub>2</sub> was significantly higher in the surfactant group 24 hours after giving surfactant associated in the same time with improvement in OI and A-a gradient. The duration of mechanical ventilation (MV), oxygen therapy and hospital stay were shorter in the surfactant group. There was no difference between two groups in the incidence of complications, need for ECMO or death.

Table (1): General characteristics of the studied sample.

	No surfactant group No = 12 (%) Mean $\pm$ SD	Surfactant group No = 12 (%) Mean $\pm$ SD	<i>t</i> -test / FET	<i>P</i> - value
<i>Gender:</i>				
Male	7 (58.3)	8 (66.7)	0.18	1.000
Female	5 (41.7)	4 (33.3)		
Gestational Age (week)	39.25 $\pm$ 0.62	39.75 $\pm$ 0.62	1.97	0.062
<i>Type of delivery:</i>				
NVD	8 (66.7)	7 (58.3)	0.18	1.000
CS	4 (33.3)	5 (41.7)		
Birth weight (gm)	3645.6 $\pm$ 342.7	3782.6 $\pm$ 271.6	1.09	0.290

Table (2): PH, PCO<sub>2</sub> and PO<sub>2</sub> values of the studied newborns.

	No surfactant group No= 12 (%) Mean $\pm$ SD	Surfactant group No= 12 (%) Mean $\pm$ SD	<i>t</i> -test	<i>P</i> - value
PH at 0 h	7.05 $\pm$ 0.09	7.11 $\pm$ 0.07	1.77	0.091
PH at 3 h	7.11 $\pm$ 0.02	7.13 $\pm$ 0.04	1.39	0.178
PH at 6 h	7.28 $\pm$ 0.03	7.32 $\pm$ 0.05	1.98	0.060
PH at 24 h	7.33 $\pm$ 0.04	7.38 $\pm$ 0.05	2.49	*0.020
PH at 48 h	7.34 $\pm$ 0.03	7.39 $\pm$ 0.04	2.89	*0.008
PaCO <sub>2</sub> at 0 h	61.5 $\pm$ 3.61	63.5 $\pm$ 2.07	1.67	0.110
PaCO <sub>2</sub> at 3 h	57.17 $\pm$ 5.86	53.50 $\pm$ 3.80	1.82	0.083
PaCO <sub>2</sub> at 6 h	52.91 $\pm$ 6.12	47.83 $\pm$ 3.48	2.45	*0.024
PaCO <sub>2</sub> at 24 h	46.0 $\pm$ 3.50	41.42 $\pm$ 2.57	3.58	*0.002
PaCO <sub>2</sub> at 48 h	42.08 $\pm$ 3.23	37.17 $\pm$ 3.88	3.37	*0.003
PaO <sub>2</sub> at 0 h	33.08 $\pm$ 6.33	35.08 $\pm$ 9.49	0.61	0.550
PaO <sub>2</sub> at 3 h	41.0 $\pm$ 12.14	50.75 $\pm$ 14.58	1.78	0.089
PaO <sub>2</sub> at 6 h	51.08 $\pm$ 4.69	57.83 $\pm$ 10.53	2.03	0.055
PaO <sub>2</sub> at 24 h	57.25 $\pm$ 11.04	67.25 $\pm$ 11.37	2.18	*0.040
PaO <sub>2</sub> at 48 h	66.5 $\pm$ 10.81	77.5 $\pm$ 7.44	2.9	*0.008

\**p*-value <0.05 is considered significant.

Table (3): MAP, OI and a-A gradient intervals of the studied newborns.

	No surfactant group No= 12 (%) Mean $\pm$ SD	Surfactant group No= 12 (%) Mean $\pm$ SD	<i>t</i> -test	<i>P</i> - value
MAP at 0 h	18.0 $\pm$ 2.37	17.5 $\pm$ 3.65	0.4	0.695
MAP at 1 h	16.13 $\pm$ 2.79	15.23 $\pm$ 3.62	0.68	0.506
MAP at 6 h	15.87 $\pm$ 3.74	12.64 $\pm$ 3.21	2.27	*0.033
MAP at 24 h	15.21 $\pm$ 3.32	12.26 $\pm$ 2.68	2.39	*0.026
MAP at 48 h	15.0 $\pm$ 4.56	11.47 $\pm$ 2.77	2.29	*0.032
OI at 0 h	32.0 $\pm$ 2.41	34.0 $\pm$ 3.16	1.74	0.096
OI at 1 h	34.01 $\pm$ 2.62	31.41 $\pm$ 3.65	1.99	0.059
OI at 6 h	29.64 $\pm$ 1.71	26.91 $\pm$ 4.44	1.98	0.060
OI at 24 h	26.17 $\pm$ 5.6	19.46 $\pm$ 4.69	3.18	*0.004
OI at 48 h	19.03 $\pm$ 3.65	13.75 $\pm$ 5.13	2.91	*0.008
a-A gradient at 0 h	565.58 $\pm$ 74.03	577.58 $\pm$ 72.77	0.40	0.693
a-A gradient at 1 h	535.58 $\pm$ 68.52	486.08 $\pm$ 85.52	1.56	0.132
a-A gradient at 6 h	436.25 $\pm$ 57.08	383.25 $\pm$ 70.14	2.03	0.055
a-A gradient at 24 h	451.75 $\pm$ 68.46	358.0 $\pm$ 82.51	3.03	*0.006
a-A gradient at 48 h	376.50 $\pm$ 77.81	272.33 $\pm$ 67.9	3.49	*0.002

\**p*-value <0.05 is considered significant.

Table (4): Outcome of the studied newborns.

	No surfactant group No= 12 (%) Mean $\pm$ SD	Surfactant group No= 12 (%) Mean $\pm$ SD	<i>t</i> -test / FET	<i>p</i> - value
Duration of MV (days)	6.17 $\pm$ 1.95	4.84 $\pm$ 1.06	2.99	*0.047
Duration of O2 therapy (days)	15.67 $\pm$ 3.72	11.92 $\pm$ 2.48	3.28	*0.043
Duration of hospital stay (days)	18.67 $\pm$ 5.42	14.61 $\pm$ 3.43	2.19	*0.039
Pneumothorax	3 (25.0)	1 (8.3)	1.20	0.590
PPHN	2 (16.7)	1 (8.3)	0.38	1.000
Sepsis	1 (8.3)	2 (16.7)	0.38	1.000
Intracranial hemorrhage	0 (0.0)	1 (8.3)	1.04	1.000
Pulmonary hemorrhage	1 (8.3)	3 (25.0)	1.2	0.590
Death	3 (25.0)	1 (8.3)	1.20	0.590
Discharge	9 (75.0)	11 (91.6)	0.25	1.000
Hemodynamic instability	3 (25.0)	1 (8.3)	1.20	0.590
Need for ECMO	3 (25.0)	1 (8.3)	1.20	0.590

MV: Mechanical ventilation. PPHN: Persistent pulmonary hypertension.

\**p*-value <0.05 is considered significant.

## Discussion

For many years treatment of MAS was mainly supportive in the form endotracheal suction trying to retrieve meconium, and respiratory support waiting for improvement of the ongoing pathology. Such management does not overcome the problem of surfactant deficiency or dysfunction [16].

Treatment of MAS was a subject for continuous research and several methods was tried over the last years. Pulmonary lavage using diluted surfactant showed good results making it a promising therapy [17].

In this study the patients received surfactant bronchoalveolar lavage had shorter duration of mechanical ventilation, shorter duration of oxygen therapy and shorter hospital stay. This was attributed to improved lung mechanics and gas exchange secondary to restoring surfactant function and reduction in the meconium induced lung pathology.

In another multicenter randomized controlled study, there was no significant reduction in duration of respiratory support in infants received surfactant lung lavage and they attributed their results to the late time of performance of lavage (average 14 hours) [2]. The peak inflammatory response that occurs in pulmonary bronchioles occurs between 12 and 24 hours after meconium aspiration. Delayed time of intervention leads to decrease in the chance to stop the ongoing pathology [18].

In this study patients received bronchoalveolar lavage showed significant improvement regarding respiratory indices. The first parameters showed improvement were PCO<sub>2</sub> and MAP (6 hours after

lavage) this can be explained by significant relief of mechanical obstruction following this procedure. Improvement in PO<sub>2</sub>, a-A gradient and OI occurred later (24 hours after lavage) due to gradual improvement in surfactant function and reduction chemical pneumonitis which may take longer time to improve.

In a study by Hui et al., 2020, there was no significant difference between both groups in the oxygen indices or length of hospital stay [19]. Actually there may be a wide variation in the degree and time of improvement following surfactant lavage this because the pathogenesis is multifactorial and factors like the onset of intrauterine aspiration and the amount of aspirated meconium cannot be accurately estimated or controlled.

Mortality rate was less in the surfactant lavage group but statistically this difference was not significant. Need for ECMO was less in the surfactant lavage group although it was also statistically not significant, but it may be important in centers where ECMO is not available. Similar results were observed by Dargaville and his colleagues [2]. In another study Hahn and his team failed to find significant effect of lung lavage using diluted surfactant on mortality or need for ECMO while they found a significant effect on the composite outcome of death or use of ECMO [20].

Similarly, another systematic review showed that surfactant lavage produced a statistically significant beneficial effect on the primary outcome of death or need for ECMO in the meta-analysis of the two randomized controlled trials [21]. This was not evident in our study and it may be due to small number of the studied patients.

There was no significant difference between lavage group and standard treatment groups in complications this may be because these complications can result from the pathophysiology of MAS itself, or secondary to mechanical ventilation taking in consideration the relatively small number of study population. Surfactant therapy itself is not without complications and side effects like hemodynamic instability, pneumothorax and intracranial hemorrhage may occur secondary to acute change in the lung compliance and subsequent hemodynamic effects [22,23].

Aiming to treat surfactant dysfunction in MAS the exogenous surfactant given may be enriched by other substances that delay its inactivation when exposed to meconium. Such substances may be surfactant proteins, phospholipids or polymers. This multimodal approach can result in better outcome [24]. Using exogenous surfactant as a treatment improves respiratory functions but does not have direct anti-inflammatory action. The inflammatory process itself will result in surfactant inactivation [25,26].

Kopincova and colleagues showed that combined use of exogenous surfactant and N-acetyl cysteine as anti-oxidative agent showed better outcome in experimentally induced MAS [27]. Mikolka and colleagues had a trial on animals and stated that combined use of budesonide added to modified porcine surfactant gives better results than use of surfactant alone including better improvement in lung functions and lower plasma levels in inflammatory mediators (IL-1beta, IL-6, IL-8 and TNF) [14].

Compared to giving surfactant bolus, bronchoalveolar lavage using diluted surfactant has advantages of homogenous distribution of surfactant throughout the lungs, using smaller surfactant dose without decreasing the effectiveness of the treatment. Moreover, bronchoalveolar lavage with surfactant enhances the removal of meconium from the lung [28,29].

Two earlier trials used bolus surfactant instead of diluted surfactant bronchoalveolar lavage showed no benefit of bolus surfactant on any significant outcome, including mortality, air leak, or duration of ventilation [30,31].

Zhu and his colleagues compared giving surfactant bolus with doing bronchoalveolar lavage with diluted porcine surfactant in full term neonates with MAS and concluded that pulmonary lavage is superior in increasing ventilation and oxygenation efficiency, shortening the duration of mechanical

ventilation, reducing the complication rate, and increasing the cure rate [32].

Several limitations of our study were evident. The intervention was not blinded from the clinical team. The small number of subjects may affect the accuracy of results.

In conclusion, lung lavage using diluted surfactant in neonates with MAS has a significant therapeutic effect and improves pulmonary functions in such patients. More clinical trials are needed to establish a clear guidelines for such treatment.

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## الغسيل الرئوي مخفض التوتر السطحي (سرفاكتانت) مقارنة بالعلاج القياسي في علاج حديثي الولادة المصابون بمتلازمة شفت العقي

كان الغرض من هذه الدراسة هو تقييم استخدام مادة سرفاكتانت المخففة في الغسيل الرئوي لحالات شفت العقي ومقارنتها بالعلاج الروتيني لمثل هذه الحالات.

شملت هذه الدراسة ٢٤ طفل يعانون من متلازمة شفت العقي وتم تقسيمهم إلى مجموعتين متساويتين المجموعة الأولى تم علاجها بالطريقة المعتادة باستخدام التهوية عالية التردد والمجموعة الثانية تم علاجها بالغسيل الرئوي باستخدام مادة (سرفاكتانت) إلى جانب التهوية عالية التردد.

تم استخدام ١٥ مل من مادة (سرفاكتانت) المخففة مقسمة إلى ٤ جرعات متساوية وحقنها في الأنبوبة الرئوية مع استخدام التهوية عالية التردد وكانت النتائج كالتالي:

المجموعة التي استخدمت (سرفاكتانت) أظهرت تحسن معتبر في ضغط ثاني أكسيد الكربون بالإضافة إلى متوسط ضغط المجرى الهوائي وذلك بعد ٦ ساعات من الحقن بينما حدث تحسن في ضغط الأوكسجين ومعامل الأوكسجين ومعامل انحدار الأوكسجين الوعائي الرئوي بعد ٢٤ ساعة كما تحسنت لدى هذه المجموعة مدة استخدام جهاز التنفس الصناعي ومدة العلاج بالأوكسجين ومدة الإقامة بالمستشفى.

لم يكن هناك اختلاف يذكر بين المجموعتين في نسبة حدوث مضاعفات أو وفيات أو استخدام جهاز ECMO.

خلاصة البحث: أن الغسيل الرئوي بمادة (سرفاكتانت) المخففة آمن وفعال في علاج حالات متلازمة شفت العقي.