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Surfactant Lavage with Lidocaine Improves Pulmonary Function in Piglets after HCl-Induced Acute Lung Injury

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Abstract

Acute respiratory distress syndrome (ARDS) is associated with significant morbidity and mortality. The pathophysiology of ARDS includes abnormalities of surfactant function as well as pulmonary inflammation. Immunomodulating drugs, like Lidocaine, have shown some success in decreasing inflammation in ARDS. We attempted to combine surfactant lavage's ability to reverse the surfactant dysfunction, while acting as a vehicle to deliver Lidocaine. Gravity-driven surfactant (Infasurf) lavage (35 ml/kg) was administered alone or mixed with Lidocaine after severe HCl acid injury (0.3N; 3cc/kg) in neonatal piglets. Treatment groups included: control (C) (n = 5), surfactant lavage (SL) (35 ml/kg-diluted Infasurf) (n = 7) and SL mixed with Lidocaine (SL+L) (n = 7). About 26–27% of the lavage was retained (phospholipid 73–74 mg/kg; Lidocaine 1.8 mg/kg). Oxygenation progressively increased in the SL and SL+L groups over the 4-hour period (at 240 min: C = 99 ± 14; SL = 154 ± 39; SL+L = 230 ± 40 mmHg) ($p < 0.05$). PaCO₂ increased in all groups from 43 ± 0.3 to 55 ± 0.7 mmHg. Only SL+L showed a reduction in PaCO₂ (at 240 min: C = 54 ± 4; SL = 53 ± 7; SL+L = 49 ± 2 mmHg) ($p < 0.05$). Finally, SL and SL + L had superior characteristics during the quasi-static pressure volume (PV) procedure as compared to Control ($p < 0.05$). In our HCl ALI model, SL improved oxygenation and quasi-static lung compliance over C. The pulmonary function effects of SL were further enhanced by the addition of Lidocaine to the surfactant suspension. Combining therapeutic agents with surfactant lavage may be an effective strategy in ALI.

Keywords

Surfactant; Infasurf; Lavage; Lidocaine; Pulmonary function; HCl acute lung injury

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Introduction

First coined in 1967 by Ashbaugh et al. [4] Acute Respiratory Distress Syndrome (ARDS) continues to be a serious disease worldwide and despite advances in modern medicine, it is associated with high mortality rates of 30–40% [7,34,43,46]. Among the various causes of ARDS, aspiration of gastric contents is one of the most common [11,15]. This has prompted the development of several animal models simulating this aspiration syndrome [12,16,20,21,32,44].

One hallmark of ARDS that has been consistently demonstrated is surfactant dysfunction [1,10,14,18,25,39,41]. Hence, administration of exogenous surfactant to patients with ARDS should reverse this surfactant dysfunction, thereby improving pulmonary function. The beneficial effect of surfactant therapy may also include a reduction in protein leak into the alveolar space and an attenuation of the lung injury [1,10,14,18,25,39,41]. Unfortunately, despite numerous animal models of ARDS demonstrating the beneficial effects of surfactant administration on pulmonary function [12,20–23,44], this success has not been translated consistently into human clinical trials of surfactant therapy. This is despite initial optimism in several published reports [1,3,10,25,34,42].

A possible explanation for the failure of surfactant replacement therapy in ARDS may relate to limitations in the method of delivery. Classically, exogenous surfactant has been administered by either bolus instillation or by nebulization. Both of these techniques have been shown to have a diminished ability to deliver surfactant uniformly when lung injury is non-homogenous, as evident in the early stages of ARDS [18,24–26]. Another novel method of surfactant delivery is by lavage administration [5,6,9,30,35,37]. Coined ‘surfactant lavage,’ it is characterized by delivering large dilute volumes of surfactant into the lungs followed by immediate drainage. This method has shown promising results in delivering surfactant uniformly, removing alveolar proteins, and improving pulmonary function [5,6,30].

Nevertheless, the animal models used in our previous experiments [5,6,30] cannot simulate the complex pathophysiological processes involved in human ARDS. Indeed, ARDS is a complex multifaceted disorder for which surfactant dysfunction is only one aspect. Direct injury to the lung can occur from the offending agent, as well as induce an inflammatory response to further aggravate the lung injury [1,10,18,25,28,29,34,41]. Therefore, any successful treatment of ARDS would ideally incorporate more than one therapeutic target.

In addition to correcting surfactant dysfunction and removing pulmonary debris, surfactant lavage may also serve as a vehicle to deliver immunomodulating drugs. We chose to combine Lidocaine with surfactant lavage. Lidocaine has shown anti-inflammatory properties when given intravenously in various rabbit models of ALI [19,31,33,45]. We theorized that the immunomodulating effects of Lidocaine would act synergistically with surfactant lavage in improving pulmonary function parameters in neonatal piglets after HCl induced ALI.

Methods

Animals

These experiments were approved by the Institutional Animal Care and Use Committee of Tripler Army Medical Center and were in compliance with the Animal Welfare Act and the National Research Council's Guide for the Care and Use of Laboratory Animals. The animals used were mixed Yorkshire piglets of either sex obtained from a local farm the morning of each experiment. These animals were 5–7 days, old weighed between 1.8 and 3.0 kg, and consisted of 10 females and 9 males.

Anesthesia was induced initially with intraperitoneal pentobarbital (30 mg/kg; Wyeth Laboratories, Philadelphia, PA) followed by orotracheal intubation with a 4.0-mm cuffed endotracheal tube. Each piglet was ventilated with a VIP Bird ventilator (Bird Products Corp., Palm Springs, CA); initial settings were a fraction of inspired oxygen (FiO_2) = 0.21, set ventilator rate = 40, inspiratory time 0.35, positive end expiratory pressure (PEEP) = 4 cm H_2O , and positive inspiratory pressure (PIP) adjusted to maintain end-tidal CO_2 (Hewlett Packard 47210A, Palo Alto, CA) between 40–45 mmHg. A femoral artery catheter was placed to continuously monitor blood pressure and to allow for arterial blood sampling. A right atrial catheter was placed to continuously monitor central venous pressure (CVP) and as a means for sampling venous blood. Both of these catheters were connected to pressure transducers (Hewlett Packard 66#M1176A6) for continuous pressure monitoring. A femoral venous catheter allowed continuous infusion of normal saline ($100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{D}^{-1}$) and administration of medications. Every 30 min sedation was maintained with intravenous pentobarbital (2.5–5 mg/kg/dose) and paralysis was obtained with intravenous pancuronium (initially 0.6 mg, then 0.3 mg hourly). A rectal probe was placed to monitor core temperature, which was maintained between 37.5–38.5°C by use of heating pads.

Pulmonary Function

Equipment included a low dead space pneumotachometer (#8313; Hans Rudolph, Kansas City, MO), an 8-French fluid-filled catheter for esophageal pressure measurements, and a PC-based data acquisition system (AT-CODAS; Dataq Instruments, Akron, OH). Measurements continuously monitored and calculated were air flow, TV, esophageal pressure, and mean airway pressure. Arterial blood gases and arterial/venous cooximeter measurements were also recorded every 30 min for the duration of the experiment.

Hemodynamic Measurements

Heart rate (HR), CVP, and mean, arterial pressure (MAP) were monitored continuously throughout the experiment.

Model

After the piglets were prepared as described above, FiO_2 was increased to 1.0. PIP was adjusted to achieve an initial PaCO_2 of 40–45 mmHg. The resultant tidal volume (TV), which was $9.3 \pm 0.4 \text{ ml/kg}$ (no difference between groups), was maintained throughout the experiment. Hemodynamic and pulmonary function measurements were recorded at 30-min intervals for the entire duration of the experiments. Initial lung injury was induced by instillation of 0.3 N HCl acid as a bolus through a feeding tube measured to the end of the ET tube through a Bodie valve (Bodie Neo2-Safe valve, BNB Medical Technologies, Inc., Orangevale, CA). HCl was administered to each side (1.5 cc/kg) serially with the animal placed on one lateral side followed by the other (60 seconds each side).

Surfactant lavage (SL) and surfactant lavage with Lidocaine (SL+L) were administered 30 minutes after injury in the respective groups. Control piglets received no treatment.

Surfactant Preparation

Infasurf (Ony Inc, New York) lavage was prepared by diluting the surfactant with normal saline to a volume of 35 ml/kg at a phospholipid concentration of 8 mg/ml. Given our prior experiences, we estimated a 30% retention, corresponding to a phospholipid dose of ~80 mg/kg.

Lidocaine Preparation

Lidocaine (Abbott Labs, N. Chicago, IL), 7 mg/kg (animal weight) was mixed with the surfactant lavage fluid. Based on the expected surfactant lavage retention of ~30%, it was estimated that a dose of 2 mg/kg of Lidocaine would be administered, similar to the initial intravenous Lidocaine dose used in previous ALI experiments [19,31,33,45].

Method for Surfactant Administration

Surfactant lavage preparations were administered by gravity through tubing connected to the endotracheal tube. Instillation was from a height of 90 cm above the head of the animal for 60 sec. The fluid was then immediately drained passively by gravity, by lowering the tubing to 90 cm below animal's head. The entire procedure lasted 120 sec, after which the piglet was reconnected to ventilator. All animals tolerated the procedure well. We have previously described this technique in detail including the hemodynamic and pulmonary effects during the lavage procedure [5].

Retained Surfactant Fluid Volume

This volume was calculated by subtracting the volume of the gravity-assisted surfactant lavage fluid drainage from the initial volume of instilled surfactant lavage.

Surfactant Analysis

Aliquots of pre-lavage samples of surfactant preparation from SL and SL+L groups were frozen at -80°C . They were later transported in dry ice to ONY, Inc (Buffalo, NY) where total surfactant was calculated as organic phospholipids [2]. Surface activity was measured on a pulsating bubble surfactometer after adjusting the concentration of the aliquot to ~3 mg/ml [13].

Quasi-static Pressure Volume (PV) Curves

Following euthanasia, each animal was disconnected from the ventilator for 5 min to allow the lungs to collapse. Quasi-static PV measurements were then obtained by recording inflation volumes in 5 cm H_2O pressure increments from 0 to 35 cm H_2O and deflation volumes back down to 0. At each pressure level, measurements were recorded after 30 sec of equilibration.

Lung Histopathology

Lungs were prepared for pathology as previously described [40]. After fixation in formalin, sections were taken from the upper, middle, and lower segments of the lung and stained with hematoxylin and eosin. Lung injury quantified using a four-point scoring system (0 = no injury, 3 = severe injury) by rating atelectasis, alveolar and interstitial reaction by a pathologist blinded to all groups.

Statistical Analysis

Data were analysed using commercial software packages (SigmaStat, SPSS Inc., Chicago, IL; JMP, Statistical Analysis System Institute, Cary, NC). Normality of data distribution was tested with by the Kolmogorov-Smirnov test. Quasi-static pressure-volume statistical comparisons were made using twoway analysis of variance (ANOVA) with post hoc orthogonal contrasts of four parts of the PV curves (initial isovolumetric 0–10 cm H_2O ; steep inflation 10–35 cm H_2O ; early isovolumetric deflation 35–20 cm H_2O ; and terminal deflation 15–0 cm H_2O). All data are presented as means $\pm$ standard errors of the mean. p values <0.05 were considered significant.

Results

There were no significant differences found among the three groups studied: Control, SL, and SL+L groups in HR, MAP, and CVP.

Retained Surfactant Fluid Volume

The percent of surfactant lavage retained in the lung, and consequently the dose of surfactant, was consistent among treatment groups. Specifically, in the SL Group, 27% was retained, yielding a calculated surfactant dose of 74.1 ± 3 mg/kg. The SL+L group retained 26% of the lavage, equating to a surfactant dose of 73.4 ± 3 mg/kg, and a Lidocaine dose of 1.8 ± 0.1 mg/kg.

Pulmonary Function

In $\text{FiO}_2 = 1.0$, the Control group had a baseline PaO_2 of 498 ± 13 mmHg, which decreased sharply to 108 ± 11 mmHg after injury. These values improved somewhat at 60–90 min after injury to 144 ± 11 mmHg, then decreased to 99 ± 14 mmHg at 240 min. The SL group started with a baseline of 493 ± 23 mmHg, and decreased to 109 ± 4 mmHg after injury. Oxygenation steadily improved with differences found over Control from 120 min ($p < 0.05$). At 240 min, PaO_2 was 154 ± 39 mmHg ($p < 0.05$). In the SL+L group, the baseline PaO_2 was 535 ± 12 mmHg, decreasing to 135 ± 15 mmHg after injury. These values were not significantly different than corresponding values in the other groups. The PaO_2 then increased progressively, achieving significance from 90 min as compared to both SL and Control, and reaching a value of 230 ± 40 mmHg by 240 min ($p < 0.05$) (Fig. 1).

PaCO_2 starting values for Control, SL, and SL+L were 43 ± 3 , 44 ± 2 , and 43 ± 1 mmHg respectively. After injury, these values increased to 56 ± 4 for Control, 54 ± 3 for SL, and 54 ± 2 mmHg for SL+L. Although Control and SL values plateaued at 54 ± 4 and 53 ± 7 mmHg respectively, PaCO_2 values for SL+L decreased significantly compared to C and SL after 120 min ($p < 0.05$) (Fig. 2).

Quasi-static Pressure Volume Curves

The initial isovolumetric portions of the curves (initial pressures from 0–10 cm H_2O) were not different among the groups. However, SL and SL+L piglets demonstrated improved lung compliance as indicated by increased volumes on steep inflation, early deflation, and terminal deflation when compared to Controls ($p < 0.05$). The magnitude of the improvement in lung compliance was similar in SL and SL+L groups (Fig. 3).

Surfactant Analysis

There were no differences in the surface tension lowering ability of the two preparations. The values at 5 min for the two groups were similar on the pulsating bubble surfactometer ($n = 3$ for each preparation).

Lung Histopathology

Lung injury scores in the Control group ranged from 1–3 ($n = 4$), the SL group ranged from 0–1 ($n = 2$), and the SL+L group ranged from 1–2 ($n = 3$). The small number of pathological specimens evaluated precludes any evaluation for significance.

Discussion

The most important finding in our study was the observation of the synergistic effect of Lidocaine when combined with exogenous surfactant lavage in improving pulmonary function

after HCl-induced lung injury in piglets. To our knowledge, this is the first study in which Lidocaine has been mixed with surfactant and administered directly into the lung. This is in contrast to reports of exogenous surfactant [12,20,21,44] or intravenous Lidocaine [33] reversing pulmonary dysfunction after HCl lung injury. Our results support the notion that combining two drugs with independent mechanisms of action directly into the lung to treat ALI has merit.

HCl instillation into the lung is an accepted method of inducing ALI [12,20,21,33,44]. To create this model, we used a higher concentration of HCl (0.3 N) than previously described [12,20,21,33,44]. Evidence of the severe ALI model was demonstrated by a sudden marked worsening in pulmonary function immediately after HCl instillation in all groups. It was also indicated by the consistent degree of injury found on histopathology. Finally, in contrast to previous studies [12,20,21,44] and to the SL+L group, the response to surfactant in the SL group was muted.

We observed the greatest difference in blood gases (PaO_2 and PaCO_2) and pressure volume characteristics in the SL+L group over and above those observed with SL alone. This supports the concept that surfactant and Lidocaine may act in synergy to improve pulmonary function. It also supports the current understanding of the multifaceted pathophysiology seen in ARDS. These abnormalities include changes in response to certain types of primary injury (chemical, infectious), evidence of surfactant depletion, surfactant dysfunction, and the presence of inflammatory markers such as cytokines [1,10,18,25,28,29,34,41]. In this animal study, we targeted two of these ARDS abnormalities in the SL+L group, demonstrating the effectiveness of combination drug therapy administered directly into the lung by lavage.

Despite Lidocaine's common usage as an anti-arrhythmic drug, increasing evidence for its anti-inflammatory effects have been reported. These include inhibition of granulocyte adherence [17,27] and inhibition of neutrophil function [36] including chemotaxis and superoxide anion (O_2^-) release [38]. The ability of Lidocaine to attenuate inflammation in ALI has been recently demonstrated in rabbits with hyperoxic [45], HCl [33], as well as endotoxin-induced ALI [31], and in a rabbit model simulating pancreatitis [19]. The attenuation in lung injury in these studies was associated with a reduction in cytokines and activated complement levels, as well as decreased wet-dry lung ratio, decreased albumin in bronchial alveolar lavage fluid, and a reduction in the sequestration of neutrophils in the lungs [19,31,33,45].

Unfortunately, the mechanism of the direct effect of Lidocaine in this model was not identified in these experiments. Our attempts to measure cytokine levels were unsuccessful on our limited bronchial alveolar lavage samples, therefore, the mechanism of the improved results with Lidocaine has yet to be determined. We can only extrapolate from previous studies and speculate how Lidocaine works in a local setting as an immunomodulating drug. We believe that in our lung injury model, the anti-inflammatory effect of Lidocaine was facilitated by the direct delivery of the drug to HCl-injured lungs by the surfactant lavage. To be sure, we can only infer that the beneficial effects of Lidocaine were due to its action as an anti-inflammatory agent. Further experiments are needed to verify this speculation. Additionally, we also did not measure the levels of Lidocaine in the serum to identify whether significant amounts are absorbed into the systemic circulation. Given the low dose and single time administration, we would speculate that systemic effects would be minimal and negligible.

To our knowledge, this is the first study to use surfactant lavage as a vehicle for delivering an immunomodulating drug. The greater improvement in pulmonary function seen in the SL+L group can serve as a potential model of drug synergy that can be exploited with other surfactant-drug mixtures, and in other models of acute lung injury. We believe surfactant lavage alone

and in combination with other therapeutic agents continues to hold promise as a clinically relevant form of pulmonary therapy for the treatment of severe acute lung injury.

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References

1. Albertson TE, Marelich GP. Pharmacologic adjuncts to mechanical ventilation in acute respiratory distress syndrome. *Crit Care Clin* 1998;14:581–610. [PubMed: 9891629]
2. Ames B. Assay of inorganic phosphate, total phosphate and phosphatases. *Methods Enzymol* 1966;8:115–118.
3. Anzueto A, Baughman RP, Guntupalli KK. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996;334:1417–1421. [PubMed: 8618579]
4. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet* 1967;2:319–323. [PubMed: 4143721]
5. Balaraman V, Sood SL, Finn KC, et al. Physiologic response and lung distribution of lavage versus bolus Exosurf in piglets with acute lung injury. *Am J Respir Crit Care Med* 1996;153:1838–1843. [PubMed: 8665043]
6. Balaraman V, Meister J, Ku TL, et al. Lavage administration of dilute surfactants after acute lung injury in neonatal piglets. *Am J Respir Crit Care Med* 1998;158:12–17. [PubMed: 9655700]
7. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824. [PubMed: 7509706]
8. Bynum LJ, Pierce AK. Pulmonary aspiration of gastric contents. *Am Rev Respir Dis* 1976;114:1129–1136. [PubMed: 1008348]
9. Cochrane CG, Revak SD, Merritt A, et al. Bronchoalveolar lavage with KL4-Surfactant in models of meconium aspiration syndrome. *Pediatr Res* 1998;44:705–715. [PubMed: 9803452]
10. Conner BD, Bernard GR. Acute respiratory distress syndrome: potential pharmacologic interventions. *Clin Chest Med* 2000;21:563–586. [PubMed: 11019728]
11. Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury. *Am J Respir Crit Care Med* 1995;152:1818–1824. [PubMed: 8520742]
12. Eijking EP, Gommers D, So KL, et al. Surfactant treatment of respiratory failure induced by hydrochloric acid aspiration in rats. *Anesthesiology* 1993;78:1145–1151. [PubMed: 8512108]
13. Enhorning G. Pulsating bubble technique for evaluating pulmonary surfactant. *J Appl Physiol* 1977;43:198–203. [PubMed: 578145]
14. Evans DA, Wilmott RW, Whitsett JA. Surfactant replacement therapy for adult respiratory distress syndrome in children. *Pediatric Pulm* 1996;21:328–336.
15. Fein AJ, Weiner-Kronish JP, Niederman M, et al. Pathophysiology of the Adult Respiratory Distress Syndrome: What have we learned from human studies? *Crit Care Clin* 1986;2:429–453. [PubMed: 3331557]
16. Folkesson HG, Matthay MA, Hebert CA, et al. Acid aspiration-induced lung injury in rabbit is mediated by interleukin-8-dependent mechanisms. *J Clin Invest* 1995;96:107–116. [PubMed: 7615779]
17. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* 2000;93:858–875. [PubMed: 10969322]
18. Holm BA, Matalon S. Role of pulmonary surfactant in the development and treatment of adult respiratory distress syndrome. *Anesth Analg* 1989;69:805–818. [PubMed: 2686493]

19. Kiyonari Y, Nishina K, Mikawa K, et al. Lidocaine attenuates acute lung injury induced by a combination of phospholipase A2 and trypsin. *Crit Care Med* 2000;28:484–489. [PubMed: 10708188]
20. Kobayashi T, Ganzuka M, Tanigushi J, et al. Lung lavage and surfactant replacement for hydrochloric acid aspiration in rabbits. *Acta Anaesthesiol Scand* 1990;34:216–221. [PubMed: 2111628]
21. Lamm WJE, Albert RK. Surfactant replacement improves lung recoil in rabbit lungs after acid aspiration. *Am Rev Respir Dis* 1990;142:1279–1283. [PubMed: 2252244]
22. Lewis JF, Ikegami M, Higuchi R, et al. Nebulized versus instilled exogenous surfactant in an adult injury model. *J Appl Physiol* 1991;71:1270–1276. [PubMed: 1757348]
23. Lewis JF, Tabor B, Ikegami M, et al. Lung function and surfactant distribution in saline lavaged sheep given instilled versus nebulized surfactant. *J Appl Physiol* 1992;1256–1264.
24. Lewis JF, Ikegami M, Jobe AH, et al. Physiologic responses and distribution of aerosolized surfactant (Survanta) in a nonuniform pattern of lung injury. *Am Rev Respir Dis* 1993;147:1364–1370. [PubMed: 8503547]
25. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1993;147:218–233. [PubMed: 8420422]
26. Lewis JF, McCaig L. Aerosolized versus instilled exogenous surfactant in a nonuniform pattern of lung injury. *Am Rev Respir Dis* 1993;148:1187–1193. [PubMed: 8239152]
27. MacGregor RR, Thorner RE, Wright DM. Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 1980;56:203–209. [PubMed: 7397378]
28. Matthay M, Rosen G. Acid respiration-induced lung injury: new insight and therapeutic options. *Am J Respir Crit Care Med* 1996;154:277–278. [PubMed: 8756794]
29. Meduri G, Headley S, Kohler G, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. *Chest* 1995;107:1062–1073. [PubMed: 7705118]
30. Meister JC, Balaraman V, Ku T, et al. Lavage administration of dilute recombinant surfactant in acute lung injury in piglets. *Pediatr Res* 2000;47:240–245. [PubMed: 10674353]
31. Mikawa K, Maekawa N, Nishina K, et al. Effect of Lidocaine pretreatment on endotoxin-induced lung injury in rabbits. *Anesthesiology* 1994;81:689–699. [PubMed: 8092515]
32. Nagase T, Ohga E, Sudo E, et al. Intercellular adhesion molecule-1 mediates acid aspiration-induced lung injury. *Am J Respir Crit Care Med* 1996;154:504–510. [PubMed: 8756829]
33. Nishina K, Mikawa K, Takao Y, et al. Intravenous Lidocaine attenuates acute lung injury induced by hydrochloric acid aspiration in rabbits. *Anesthesiology* 1998;88(5):1300–1309. [PubMed: 9605691]
34. Notter RH, Apostolakos M, Hohn BA, et al. Surfactant therapy and its potential use with other agents in terms of infants, children, and adults with acute lung injury. *Perspect Neonatol* 2000;1:4–20.
35. Ohama Y, Ogawa Y. Treatment of meconium aspiration syndrome with surfactant lavage in an experimental rabbit model. *Pediatr Pulmonol* 1999;28:18–23. [PubMed: 10406046]
36. Ohsaka A, Saionji K, Sato N, et al. Local anesthetic lidocaine inhibits the effect of granulocyte colony-stimulating factor on human neutrophil functions. *Exp Hematol* 1994;22:460–466. [PubMed: 7513653]
37. Paranka MS, Walsh WF, Stancombe BB. Surfactant lavage in a piglet model of meconium aspiration syndrome. *Pediatr Res* 1992;31:625–628. [PubMed: 1635826]
38. Sasagawa S. Inhibitory effects of local anesthetics on migration, extracellular release of lysosomal enzyme, and superoxide anion production in human polymorphonuclear leukocytes. *Immunopharmacol Immunotoxicol* 1991;13:607–622. [PubMed: 1663527]
39. Seeger W, Günther A, Walmrath HD, et al. Alveolar surfactant and adult respiratory distress syndrome: pathogenic role and therapeutic prospects. *Clin Invest* 1993;71:177–190.
40. Sood SL, Balaraman V, Finn KC, et al. Exogenous surfactants in a piglet model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996;153:1309–1315. [PubMed: 8616559]
41. Spragg RG. Surfactant replacement therapy. *Clin Chest Med* 2000;21(3):531–541. [PubMed: 11019725]
42. Spragg RG, Harris KW, Lewis J, et al. Surfactant treatment of patients with ARDS may reduce acute lung inflammation (abstract). *Am J Respir Crit Care Med* 2001;163:A23.

43. Steinberg KP, Hudson LD. Acute lung injury and acute respiratory syndrome, the clinical syndrome. *Clin Chest Med* 2000;21:401–417. [PubMed: 11019717]
44. Strohmaier W, Redl H, Schlag G. Studies of the potential role of a semi-synthetic surfactant preparation in an experimental aspiration trauma in rabbits. *Exp Lung Res* 1990;16:101–110. [PubMed: 2328709]
45. Takao Y, Mikawa K, Nishina K, et al. Lidocaine attenuates hyperoxic lung injury in rabbits. *Acta Anaesthesiol Scand* 1996;40:318–325. [PubMed: 8721462]
46. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342:1334–1349. [PubMed: 10793167]

Fig. 1.

Effects of HCl instillation and subsequent treatment with surfactant lavage on PaO₂ in Control, SL and SL+L groups. All data are presented as mean $\pm$ standard error. SL and SL+L groups showed improvement in oxygenation with time starting at 90 min (* $p < 0.05$). Further, oxygenation in the SL group was better than Controls starting at 120 min ($^{\dagger}p < 0.05$). Oxygenation in the SL+L group was better than the other two groups starting at 90 min ($^{\S}p < 0.05$).

Fig. 2.

Effects of HCl instillation and subsequent treatment with surfactant lavage on PaCO₂ in Control, SL and SL+L groups. All data are presented as mean $\pm$ standard error. PaCO₂ decreased only in the SL+L group with time starting at 120 min (* $p < 0.05$) and this was significantly different compared to the other groups ($^{\dagger}p < 0.05$).

Fig. 3.

Results of Quasi-static pressure volume measurements in the Control, SL and SL+L groups. Improvement in pressure volume characteristics are seen on inflation (15–35 cm H₂O), early deflation (35–20 cm H₂O), and steep deflation (15–0 cm H₂O) portions in SL+L and SL over Controls (**p* < 0.05).