ORIGINAL ARTICLES

Nebulisation of surfactants in an animal model of neonatal respiratory distress

Tai Fai Fok, Mazen Al-Essa, Myrna Dolovich, Farid Rasid, Haresh Kirpalani

Abstract

***Aims*—To evaluate pulmonary deposition and gas exchange following nebulisation of two surfactants by either a jet or an ultrasonic nebuliser.**

***Method*—After bronchoalveolar lavage (BAL), 19 rabbits were ventilated in four groups. Group A1 (n=5) and A2 (n=6) received Technetium-99m labelled Exosurf, and groups B1 (n=4) and B2 (n=4) received radiolabelled Survanta. Groups A1 and B1 received jet nebuliser therapy, whereas groups A2 and B2 received ultrasonic nebuliser. Pulmonary deposition, distribution, and blood gases were determined.**

***Results*—Pulmonary deposition as per cent of initial dose and mg lipid) was 0.28(0.10)% or 0.59(0.21) mg in group A1, 1.05(0.23)% or 2.21(0.48) mg in group A2, 0.08(0.02)% or 0.30(0.08) mg in group B1, and 0.09(0.02)% or 0.34(0.08) mg in group B2. Deposition in group A2 was greater than in other groups (p= 0.001). Group A2 showed a small improvement in blood gases.**

***Conclusions*—Even the highest deposition—ultrasonic nebuliser with Exosurf—achieved limited clinical effect. The aerosol route is currently not effective for surfactant treatment.**

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Keywords: surfactant; nebuliser; respiratory distress syndrome; rabbits

Department of Paediatrics
T Fok
M Al-Essa
H Kirpalani

Department of Medicine
M Dolovich

Department of Nuclear Medicine McMaster University Medical Centre, Hamilton, Ontario, Canada
F Rasid

Correspondence to:
Dr H Kirpalani
Department of Paediatrics
McMaster University
1200 Main Street West
Hamilton, Ontario, Canada
L8N 3Z5.

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Intratracheal instillation of exogenous surfactant is standard treatment in preterm babies with respiratory distress syndrome (RDS).[1] Studies have also been performed to examine the effect of surfactant in full term infants with other conditions, such as pneumonia and meconium aspiration syndrome,[2–5] and in children and adults with acute respiratory distress syndrome (ARDS).[6–8] To achieve uniform distribution in the lungs, surfactant should be given rapidly and in relatively large volumes,[9 10] but rapid intratracheal administration of a large volume of the medication may cause transient hypoxia, hypercapnia, changes in cerebral blood flow velocity and intraventricular haemorrhage.[11 12] The technique may be poorly tolerated by unstable infants such as those with persistent pulmonary hypertension. An alternative route of administration may thus be desirable. Over a decade ago Marks *et al* showed that both jet and ultrasonic nebulisers could deliver phospholipids extracted from bovine lung lavage without changing their surface active properties.[13] In a variety of animal models of induced lung injury, nebulised surfactant improved both ventilation and lung mechanics, even with minimal deposition in the lungs.[14–18] One large scale study, however, showed that nebulised surfactant did not improve the outcome of adult patients with ARDS.[19]

At present, therapeutic aerosols are administered to ventilated infants most commonly with a jet nebuliser. Studies in adults show that only a maximum of 2.9% of the nebuliser dose is deposited in the lungs by this form of nebulisation.[20–22] Deposition in ventilated newborns is even lower, being less than 2% of the aerosol released into the ventilator circuit.[23–29] Recent in vitro and in vivo evidence suggests that ultrasonic nebulisers are more efficient than jet nebulisers in delivering therapeutic aerosols to both adults and infants.[30–32] This study was therefore carried out to evaluate the efficiency of a jet and an ultrasonic nebuliser in delivering both a synthetic and an animal surfactant to a neonatal lung model of surfactant deficiency under standardized experimental conditions.

Methods

The animal model consisted of an adult White New Zealand rabbit whose pulmonary endogenous surfactant was depleted by broncheoalveolar lavage (BAL). The study was approved by the Animal Ethics Committee of McMaster University. The animal was anaesthetised using intramuscular ketamine (40 mg/kg) and xylazine (5 mg/kg), and ventilated with a continuous flow infant ventilator (Bournes BP200, USA) through an endotracheal tube (internal diameter 3.5 mm) inserted into the trachea through a tracheostomy. An intravenous line and an arterial line were established for infusion of 10% dextrose and blood gas monitoring, respectively. After paralysing the animal with Pancuronium 100 µg/kg, BAL was performed with warm (37°C) physiological saline (25 ml/kg) infused into the lungs over 10 seconds at a hydrostatic pressure of 30 cm

Table 1 Body weight before and after BAL, PaO_2, $PaCO_2$ of animals (mean (SEM))

	Group A (Exosurf)		Group B (Survanta)	
Parameters	*A1 (jet)*	*A2 (ultrasonic)*	*B1 (jet)*	*B2 (ultrasonic)*
Body weight (g)	2894 (63)	2933 (59)	2957 (51)	3020 (78)
PaO_2 (mm Hg):				
Before BAL	297.5 (44.2)	309.3 (35.7)	319.4 (33.8)	323.5 (15.2)
After BAL	39.0 (4.8)	36.2 (2.4)	49.8 (2.1)	50.1 (9.1)
p (paired t test)	0.0048	0.0006	0.0055	0.0008
After nebulisation (mins):				
0	37.4 (2.1)	39.2 (1.8)	37.0 (3.2)	52.3 (8.6)
30	43.4 (5.0)	49.5 (6.0)	40.3 (3.6)	62.1 (17.1)
60	50.9 (7.2)	71.7 (5.7)	55.1 (15.5)	45.3 (9.1)
p (ANOVA)	0.148	0.001	0.452	0.239
$PaCO_2$ (mm Hg):				
Before BAL	39.0 (4.4)	34.6 (3.2)	34.2 (6.3)	37.9 (3.0)
After BAL	59.1 (4.2)	53.8 (5.6)	60.0 (1.5)	55.1 (6.7)
p (paired t test)	0.027	0.014	0.0081	0.042
After nebulisation (mins):				
0	56.6 (2.5)	61.0 (4.0)	67.1 (7.4)	51.3 (10.0)
30	58.8 (7.1)	55.8 (3.4)	68.9 (8.3)	51.2 (8.8)
60	56.8 (5.2)	50.1 (1.8)	62.6 (15.2)	57.7 (9.5)
p (ANOVA)	0.845	0.0066	0.926	0.108

Table 2 Nebuliser output and pulmonary deposition of surfactant aerosol

	Aerosol output		Pulmonary deposition		
Group	*As % nebuliser dose*	*As mg lipid*	*As % output*	*As % nebuliser dose*	*As mg lipid*
Exosurf					
A1 (jet)	47.0 (6.7)	98.7 (14.7)	0.61 (0.17)	0.28 (0.10)	0.59 (0.21)
A2 (ultrasonic)	27.5 (2.3)	57.8 (4.9)	3.6 5 (0.56)	1.05 (0.23)	2.21 (0.48)
p (unpaired t test)	0.016	0.019	0.001	0.019	0.010
Survanta					
B1 (jet)	7.9 (0.9)	29.6 (3.4)	0.94 (0.16)	0.08 (0.02)	0.30 (0.08)
B2 (ultrasonic)	2.5 (0.3)	9.4 (1.1)	3.88 (0.93)	0.09 (0.02)	0.34 (0.08)
p (unpaired t test)	0.001	0.001	0.021	0.687	0.736
Comparing all four groups (ANOVA)	< 0.0001	< 0.0001	0.0003	0.001	0.0017
Student-Newman-Keul test ($p < 0.05$)	A1>A2>B1&B2	A1>A2>B1&B2	A2&B2> A1&B1	A2>all others	A2>all others

water, and then allowed to drain out of the lungs under gravity. This procedure was performed four times with the animal supine and twice more after turning the animal prone. The whole procedure took about 30 minutes. After BAL had started ventilator settings were adjusted to give a peak inflation pressure of 25cm water, positive end expiratory pressure 4 cm water, rate 30/minute, inspiratory time 0.5 seconds, and 100% oxygen. The same ventilator settings were used throughout the entire experiment and in all animals. An absolute filter (Pall Biomedical, NY, USA) was connected to the expiratory limb of the ventilator circuit to prevent the contamination of the ventilator and the environment by the radiolabelled aerosol.

Nebulisation was carried out 1 hour after the completion of BAL. Fifteen ml of either Exosurf (Burroughs Wellcome Laboratories, Canada), a synthetic surfactant containing 14 mg phospholipid per ml, or Survanta, a natural surfactant containing 25 mg phospholipid per ml, was placed in the nebuliser, and nebulisation was continued for 1 hour. The surfactants were labelled with Technetium-99m (^{99m}Tc),[33] and each ml contained about 280 μCi of radioactivity. A total of 19 rabbits were studied. Group A was given ^{99m}Tc-Exosurf by either a jet nebuliser (Up-Mist Medication Nebuliser, Hospitek, USA) (group A1 n=5) or an ultrasonic nebuliser (Siemens Electronics Inc., Sweden) (group A2 n=6). The same nebulisers were used to deliver ^{99m}Tc-Survanta to group

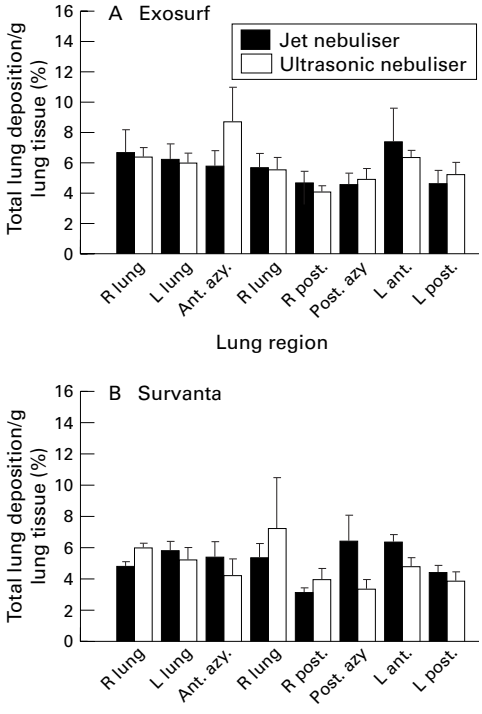

Figure 1 Pulmonary distribution of 99m Technetium labelled (A) Exosurf and (B) Survanta delivered by jet or ultrasonic nebuliser. Each bar represents deposition per gram lung tissue, expressed as mean (SEM) percentage of total lung deposit. A: anterior azygous lobe; b: right anterior lobe; c: right posterior lobe; d: posterior azygous lobe; e:left anterior lobe; f: left posterior lobe; g:both lungs.

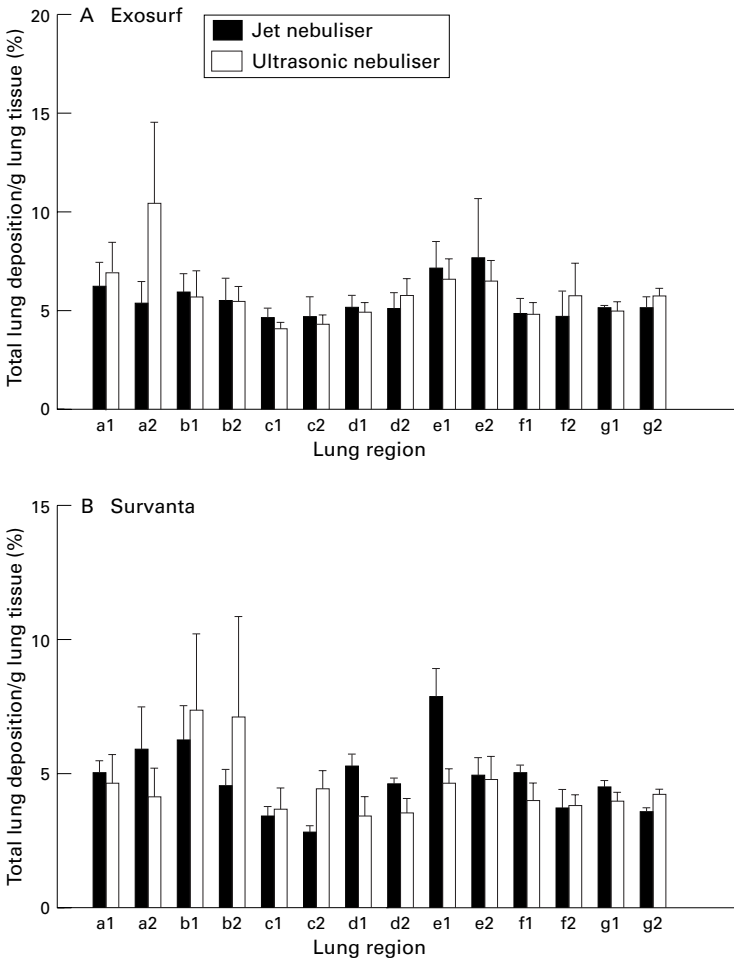

Figure 2 Pulmonary distribution of 99m Technetium labelled (A) Exosurf and (B) Survanta delivered by jet or ultrasonic nebuliser. Each bar represents deposition per gram lung tissue, expressed as mean (SEM) percentage of total lung deposition.

Table 3 Deposition of surfactant in airway and ventilator circuit (as % of amount nebulised): mean (SEM)

Group	*Trachea and carina*	*Inspiratory circuit**
Exosurf		
A1 (jet)	0.20 (0.08)	12.79 (3.20)
A2 (ultrasonic)	1.97 (0.48)	9.83 (1.81)
B1 (jet)	0.13 (0.01)	11.21 (1.96)
B2 (ultrasonic)	1.57 (0.46)	7.25 (0.47)
p (ANOVA)	0.004	0.407
Student-Newman-Keul test ($p < 0.05$)	A2 and B2>A1 and B1	

* Inspiratory tubing+endotracheal tube+endotracheal tube connector+Y-connector.

B1 (jet nebuliser n=4) and group B2 (ultrasonic nebuliser n=4).

The nebulisers were connected to the inspiratory limb of the ventilator circuit 20 cm away from the Y-connector of the endotracheal tube. The jet nebuliser, connected by 10 cm tubing into the inspiratory line, was operated using pure oxygen at a flow rate of 6 litres/minute, as recommended by the manufacturer. During nebulisation, the gas flow rate from the ventilator was reduced accordingly so as to maintain the same peak inflation pressure. The ultrasonic nebuliser, inserted directly into the inspiratory line, required no external gas source and therefore did not require adjustment of the ventilator flow rate. Throughout the entire experiment, the ventilator tubings were positioned below the animals to ensure that surfactant condensed inside the ventilator tubings did not drain into the lungs. Arterial blood gas was determined before and after BAL, and repeated just before, at 30 minutes, and on completion of nebulisation. The accumulation of radioactivity in the lungs was monitored continuously with a gamma camera (Model 410 LFOV, Ohio Nuclear, USA) throughout nebulisation.

From observations in preliminary studies, we suspected that some of the surfactant condensed inside the ventilator tubings might drain into the lungs, resulting in overestimation of aerosol deposition. In order to test the hypothesis we studied four additional rabbits (group C) who were given nebulised Exosurf with an ultrasonic nebuliser in the same way and for the same duration as those in group A2. However, the ventilator tubings in these rabbits were positioned in the more traditional manner with the terminal part of the tubings at a level slightly higher than that of the animals.

After completion of nebulisation the animals were sacrificed with intravenous pentobarbitone and the lungs excised. Each lung lobe was dissected from its main bronchus and divided into approximately equal peripheral (subpleural) and central (perihilar) portions. Each lung specimen was weighed on an electronic scale. The trachea was divided from the main bronchi just above the carina.

The radioactivity in the endotracheal tube, the trachea, the carina region, and each lung piece was measured using a gamma counter (Minaxi Auto-Gamma 5000R, Canada) with corrections made to allow for decay between manufacture of the tracer and counting. This allowed us to calculate the amount of surfactant deposited in each specimen. Radioactivity in different parts of the ventilator circuit was determined with a dose calibrator (Capintec Inc., Pittsburg, USA). The radioactivity inside the nebuliser before and after nebulisation was also measured for calculation of aerosol output.

The particle size distribution of the surfactant aerosols exiting the endotracheal tube was measured using the Aerosizer (Amherst Process Instruments, Hadley, MA, USA). Aerosols were introduced into the sampling area of the instrument using a 23 litre sampling sphere and particle size distribution was expressed as mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

All values were expressed as mean (SEM). The paired and unpaired *t* tests were used for comparison of dual values within the same group, and values between two groups, respectively. For comparing more than two groups, the one way analysis of variance (ANOVA) was used. Aerosol distribution among different lung regions in the same group was compared using one way repeated measures ANOVA. When the ANOVA test showed a significant difference, the Student-Newman-Keul method was used for isolation of group or groups that differed from others.

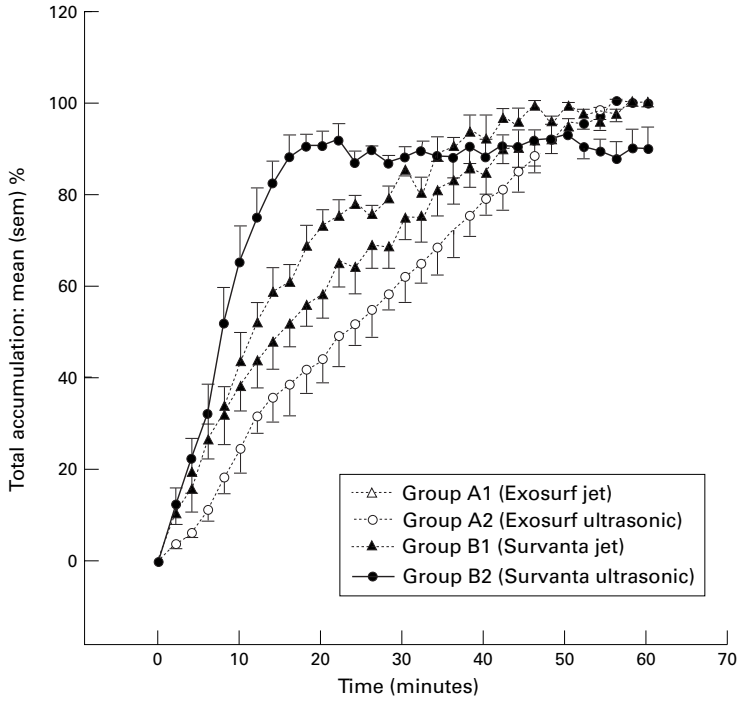

Figure 3 Dynamic gamma scintigraphy showing accumulation of the ^{99m}Tc labelled surfactant in the lungs during nebulisation by jet or ultrasonic nebuliser. Y axis represents radioactivity accumulated in the lungs, expressed as mean (SEM) percentage of the final total radioactivity deposited in the lungs.

Results

DESCRIPTION OF ANIMALS AND AEROSOL PARTICLE SIZE

There were no significant differences in the following measurements among animals in group A1, A2, B1 and B2: body weight (p=0.60), before and after BAL PaO_2 (before BAL: p=0.96; after BAL: p=0.283) and $PaCO_2$ (before BAL: p=0.844; after BAL: p=0.799). All the animals were rendered significantly hypoxic and hypercapnoeic after BAL (table 1).

The mean (SEM) MMAD and GSD of Exosurf aerosol generated by the jet and ultrasonic nebuliser were 0.74 (0.05) μm (GSD 1.37[0.002]) and 1.23 (0.16) μm (GSD 1.52[0.08]), respectively. Corresponding values of the Survanta aerosol were 0.90 (0.06) μm (GSD 1.42[0.04]) from the jet nebuliser and 2.10 (1.75) μm (GSD 1.73[0.65]) from the ultrasonic nebuliser.

DELIVERY OF SURFACTANT AEROSOL

After 1 hour of nebulisation, the total dose of Exosurf aerosolised from the jet nebuliser was significantly greater than that from the ultrasonic nebuliser (table 2). Similarly, nebulisation of Survanta was more efficient using the jet nebuliser than the ultrasonic nebuliser. For both types of nebuliser, the output of Survanta aerosol was small and significantly less than that of Exosurf (p<0.001 for both nebulisers).

Aerosol delivery to the lung also varied both with the type of nebuliser and surfactant used (table 2). There was a significant difference among the four groups in terms of the percentage of the aerosol output, the percentage of the initial nebuliser dose, and mg of lipid deposited. Despite the lower rate of aerosol production, Exosurf nebulised by the ultrasonic nebuliser (group A2) achieved the greatest lung deposition, although the total amount deposited was still only 1% of the initial nominal dose.

DISTRIBUTION OF SURFACTANT

Surfactant distribution in the various lung regions was calculated from the deposition per gram lung tissue, expressed as a percentage of total lung deposition. With either surfactant preparation and either nebuliser, there was no significant difference in distribution between the right and left lungs (group A1: p=0.788; A2: p=0.738; B1: p=0.293; B2: p=0.505), or among the lung lobes (group A1: p=0.630; A2: p=0.117; B1: p=0.163; B2: p=0.611) (fig 1). In all the groups distribution to the peripheral and central regions also did not differ significantly in each lobe and also in both lungs (group A1: p=0.0916; A2: p=0.381; B1: p=0.082; B2: p=0.543) (fig 2). Table 3 shows the distribution of surfactant in the airway and inspiratory ventilator circuit. The ultrasonic nebuliser deposited more of the surfactants at the trachea and carina but deposition in the inspiratory circuit did not show any significant difference.

DYNAMIC GAMMA SCINTIGRAPHY STUDY

The accumulation of radioactivity in the lungs during nebulisation is shown in fig 3. In the

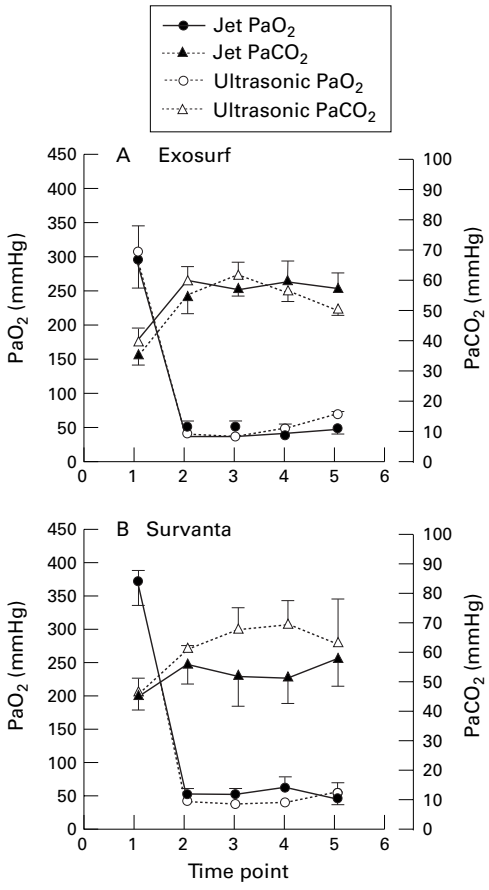

Figure 4 Blood gas changes associated with BAL and delivery of (A) Exosurf or (B) Survanta aerosol by jet or ultrasonic nebuliser. (1): before BAL; (2): immediately after BAL; (3): immediately before surfactant treatment; (4): 30 minutes and (5): 60 minutes after surfactant treatment.

Exosurf groups pulmonary accumulation of radioactivity delivered by either the jet or ultrasonic nebuliser had an almost linear correlations with the duration of nebulisation up to the end of the 60 minute period. In the Survanta groups the accumulation curve from the jet nebuliser was similar in pattern to those seen in the Exosurf groups. The pattern was, however, very different in the group of animals receiving the radiolabelled Survanta from the ultrasonic nebuliser (group B2). There was an initial phase of rapid accumulation which lasted for about 20 minutes. After this initial phase the accumulation curve levelled off, suggesting that there was no further deposition of the surfactant in the lungs after the first 20 minutes.

BLOOD GAS CHANGES

All groups of animals showed a significant drop in PaO_2 and rise in $PaCO_2$ after BAL (table 2 and fig 4). The blood gases after BAL showed that animals who were given Exosurf by the ultrasonic nebuliser (group B1) had a significantly higher $PaCO_2$ and $PaCO_2$ at the end of nebulisation (time point 5) than at the beginning (time point 3). No significant changes in the PaO_2 or $PaCO_2$ readings before or after BAL were observed in any of the other groups.

EFFECT OF VENTILATOR TUBING POSITION ON PULMONARY DEPOSITION

When Exosurf aerosol was delivered by the ultrasonic nebuliser with the ventilator tubings positioned at a slightly higher level than that of the animals (group C, weight 2782 (76) g), 41.19 (7.26)% of the total amount of surfactant placed in the nebuliser was nebulised into the ventilator circuit. This was greater than the aerosol output observed in group A2, although the difference did not reach significance ($p=0.066$). Surfactant deposition in the lungs of this group was 4.42 (1.34)% of the initial nebuliser dose or 8.87 (2.82) mg of lipid. Both were significantly greater than those in group A2 ($p<0.0001$ and $p=0.0006$, respectively).

The distribution of surfactant among the lung lobes in group C also differed from that in group A2. A significantly greater proportion (11.91 [3.19]% per g lung tissue) of the total pulmonary deposition was deposited in the right upper lobe while the relative amount deposited in the other lobes ranged only from 2.28 (0.73)% per g lung tissue to 5.77 (3.12)% per g lung tissue ($p=0.026$).

Discussion

In ventilated animal models of lung injury, Lewis *et al* have shown that pulmonary deposition of nebulised natural surfactants ranged from 1.9% to 15% of the initial nebuliser dose, the greatest deposition being observed in large animals (adult sheep) weighing about 40 kg.[15] In small animals (rabbit and preterm lamb) deposition was relatively small, but even the smallest deposition of 1.9% was associated with improvement in lung mechanics and oxygenation status of the animals.[17 18] In a rat model Li *et al* have shown that nebulised natural surfactant can reverse respiratory failure induced by BAL.[34] Both groups of workers have, however, used manoeuvres that are not standard in neonatal ventilation. Lewis *et al* used a signal actuated nebuliser and volume cycled ventilators not usually deployed for infants, and prolonged nebulisation for 3 hours which might be too long to fit into the neonatal intensive care unit routine. Both groups ventilated the animals with high inflation pressures and long inspiratory times, and intermittently reloaded the nebuliser with fresh surfactant throughout nebulisation. Despite higher depositions, the net result is a large consumption of surfactant and may not be an economical way to use this expensive medication. In this study, we used ventilator settings commonly used on newborns and small infants to evaluate the delivery of a synthetic and a natural surfactant by a jet and ultrasonic nebuliser.

Our findings show that pulmonary deposition of aerosolised surfactant is greatly affected by the type of surfactant and nebuliser used. Output of Exosurf aerosol from either the jet or ultrasonic nebuliser was 6 to 10 times greater than that of Survanta aerosol. This difference in aerosol output may be a result of the different composition and viscosity of the two surfactants. Exosurf does not contain protein and behaves similarly to a fine particle liposome while the protein content of Survanta, which improves its functional ability, may make it more difficult to be aerosolised.[35] In addition, the greater phospholipid content in Survanta may have contributed to the reduced nebulisation efficiency with both types of nebulisers. Aerosol output is inversely related to the viscosity of the nebulised solution.[36] Survanta seems to be a much more viscous solution than Exosurf, although we do not have information on the viscosity of the two preparations. Evaporation of the aqueous component of a viscous solution during nebulisation further increases its concentration and viscosity, and can eventually lead to cessation of aerosolisation.[36] At the end of nebulisation, the appearance of the remaining Survanta in the nebulisers was indeed similar to white glue. This phenomenon may provide an explanation for the shape of the dynamic scintigraphy curves which show that delivery of the radiolabelled Survanta aerosol by the ultrasonic nebuliser virtually ceased after the first 20 minutes (fig 4). In contrast, the jet nebuliser seemed to be less susceptible to the concentrating effect, and continued to aerosolise the surfactant up to the end of the one hour period effecting a linear correlation with time. This pattern of accumulation was similar to that seen in the animals receiving Exosurf from either the jet or the ultrasonic nebuliser.

Our findings also show that although the jet nebuliser was able to generate larger aerosol outputs, the ultrasonic nebuliser was more efficient in depositing the aerosol in the animals' airway, and the greatest amount of pulmonary deposition was observed in animals receiving Exosurf from this device. The discrepancy did not seem to have resulted from differences in aerosol impaction at the inspiratory tubings or

endotracheal tube, as shown by the data on fractional deposition at ventilator circuit. The jet nebuliser we used produced a submicronic aerosol. These small particles might have failed to deposit in the lower respiratory tract but might have been exhaled and lost to the expiratory tubings and filters. Inefficient delivery of submicronic aerosols by jet nebulisers have also been reported by other workers.[27] With both surfactants and both types of nebuliser, aerosol reaching the animals' lungs were evenly distributed among the lung lobes and also the peripheral and central lung regions. This agreed with the observation of Lewis *et al* in animals with uniform lung injury.[16]

We did not observe any clinically relevant therapeutic effect of either Exosurf or Survanta delivered by the jet nebuliser (groups A1 and B1), or of Survanta delivered by the ultrasonic nebuliser (group B2). This could be attributed to the very small surfactant deposition in the lungs of animals in these groups. Animals in group A2 received Exosurf from the ultrasonic nebuliser and had the greatest amount of lung deposition. Only in this group was there any improvement in blood gases. The improvement, although significant, was relatively small when compared with the findings of Lewis *et al*, who showed a dramatic improvement in oxygenation and lung mechanics in animals with acquired lung injury following treatment with nebulised surfactant.[14–18] There are a few possible explanations for this discrepancy: our animals were rendered much more hypoxic and acidotic than those in Lewis' studies, and the more severe lung injury might have made the lungs less responsive to the surfactant; the synthetic surfactant (Exosurf) received by our animals might be less potent and have a slower action than the natural surfactants used by Lewis *et al*.[16] In a recent large randomised trial in adults with sepsis induced ARDS, aerosolised Exosurf also failed to show any beneficial effects,[19] although improvement has been shown in similar patients treated with natural surfactants[37 38] given by either brochoscope or simply instilled. This last is a randomised trial in adults, aimed at dose definitions, which found a reduction in mortality at doses of 100 mg phospholipid/kg times four, when this was simply instilled.[38]

A comparison of the group A2 and group C animals provides some insights into the importance of gravity on surfactant aerosol delivery. Both groups received Survanta aerosol from the ultrasonic nebuliser, and differed only in the relative position of the ventilator tubings to the animals. In group C, the higher position of the terminal part of the ventilator tubings was associated with greatly increased lung deposition, suggesting that surfactant condensed inside the tubings might have rained down the animals' lungs. The different distribution pattern of surfactant in their lungs also suggested that part of the surfactant might have been delivered by an alternative route. This observation should serve to remind researchers not to overlook the importance of gravity in surfactant aerosol studies.

In conclusion, we have shown that both the jet and ultrasonic nebuliser were inefficient in delivering Survanta aerosol. In the delivery of Exosurf, the ultrasonic nebuliser was better than the jet nebuliser, but even in this group lung deposition was only 1% of the initial dose. Only this group showed some small, albeit significant, improvement in blood gases. Until technical breakthrough in nebuliser design occurs, the aerosol route does not seem to be appropriate for surfactant replacement or supplementation in ventilated infants.

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1 Soll RF, Sinclair JC, Bracken MB. Meta-analysis of surfactant trials: the effect of prophylactic surfactant vs surfactant treatment of established RDS. *Pediatr Res* 1993;**33**:276A.
2 Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full term neonates with severe respiratory failure. *Pediatrics* 1993;**92**:135-9.
3 Auten RL, Notter RH, Kendig JW, Davis JM, Shapiro DL. Surfactant treatment of full-term newborns with respiratory failure. *Pediatrics* 1991;**87**:101-7.
4 Findlay RD, Taeusch HW, Walther FJ. Surfactant therapy for meconium aspiration syndrome. *Pediatrics* 1996;**97**:48-52.
5 Shindler M, Bohn D, Bryan C, Barker G. The effect of surfactant in pediatric patients with respiratory failure. *Clin Invest Med* 1992;**15**:108A.
6 Richman PS, Spragg RG, Robertson B, Merritt TA, Curstedt T. The adult respiratory distress syndrome: first trials with surfactant replacement. *Eur Respir J* 1989;**3(Suppl)**:109-11.
7 Weg JG, Balk RA, Tharratt RS, *et al*. Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress syndrome. *JAMA* 1994;**272**:1433-8.
8 Lachmann B. Animal models and clinical pilot studies of surfactant replacement in adult respiratory distress syndrome. *Eur Respir J* 1989;**3 (Suppl)**:98-103.
9 Van Der Bleek J, Plotz FB, Van Overbeek FM, *et al*. Distribution of exogenous surfactant in rabbits with severe respiratory failure: the effect of volume. *Pediatr Res* 1993;**34**:154-8.
10 Segerer H, Van Gelder W, Angenent FW, *et al*. Pulmonary distribution and efficacy of exogenous surfactant in lung-lavaged rabbits are influenced by the instillation technique. *Pediatr Res* 1993;**34**:490-4.
11 Cowan F, Whitelaw A, Wertheim D, Silverman M. Cerebral blood flow velocity changes after rapid administration of surfactant. *Arch Dis Child* 1991;**66**:1105-9.
12 Gunkel JH, Banks PL. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. *Pediatrics* 1993;**92**:775-86.
13 Marks LB, Notter RH, Oberdorster G, McBridge JT. Ultrasonic and jet aerosolization of phospholipids and the effects on surface activity. *Pediatr Res* 1993;**17**:742-7.
14 Lewis JF, Ikegami M, Jobe AH, Absolom D. Physiologic responses and distribution of aerosolized surfactant (Survanta) in a nonuniform pattern of lung injury. *Am Rev Respir Dis* 1993;**147**:1364-70.
15 Lewis JF, McCaig L. Aerosolized versus instilled exogenous surfactant in a nonuniform pattern of lung injury. *Am Rev Respir Dis* 1993;**148**:1187-93.
16 Lewis JF, Tabor B, Ikegami M, Jobe AH, Joseph M, Absolom D. Lung function and surfactant distribution in saline-lavaged sheep given instilled vs. nebulised surfactant. *J Appl Physiol* 1993;**74**:1256-64.
17 Lewis JF, Ikegami M, Jobe AH, Tabor B. Aerosolized surfactant treatment of preterm lambs. *J Appl Physiol* 1991;**70**:869-76.
18 Lewis J, Ikegami M, Higuchi R, Jobe A, Absolom D. Nebulised vs. instilled exogenous surfactant in an adult lung injury model. *J Appl Physiol* 1991;**71**:1270-6.
19 Anzueto A, Baughman RP, Guntupalli KK, *et al*. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996;**334**:1417-21.
20 Thomas SH, O'Doherty MJ, Fidler HM, Page CJ, Treacher DF, Nunan TO. Pulmonary deposition of a nebulised aerosol during mechanical ventilation. *Thorax* 193;**48**:154-9.
21 Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients. Comparison of dose to the lungs. *Am Rev Respir Dis* 1990;**141**:440-4.
22 MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman E. Aerosol delivery in intubated, mechanically ventilated patients. *Crit Care Med* 1985;**13**:81-4.

23 Cameron D, Arnot R, Clay M, Silverman M. Aerosol delivery in neonatal ventilator circuits: a rabbit lung model. *Pediatr Pulmonol* 1991;**10**:208-13.
24 Arnon S, Grigg J, Nikander K, Silverman M. Delivery of micronized budesonide suspension by metered dose inhaler and jet nebuliser into neonatal ventilator circuit. *Pediatr Pulmonol* 1992;**13**:172-5.
25 Grigg J, Arnon S, Jones T, Clarke A, Silverman M. Delivery of therapeutic aerosols to intubated infants. *Arch Dis Child* 1992;**67**:25-30.
26 Watterberg KL, Clark AR, Kelly HW, Murphy S. Delivery of aerosolized medication to intubated babies. *Pediatr Pulmonol* 1991;**10**:136-41.
27 Cameron D, Clay M, Silverman M. Evaluation of nebulizers for use in neonatal ventilator circuits. *Crit Care Med* 1990;**18**:866-70.
28 Flavin M, MacDonald M, Dolovich M, Coates G, O'Brodovich H. Aerosol delivery to the rabbit lung with an infant ventilator. *Pediatr Pulmonol* 1986;**2**:35-9.
29 Fok TF, Monkman S, Dolovich M, *et al*. Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebuliser in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1996; **21**:301-9.
30 Thomas SHL, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulised aerosols to a lung model during mechanical ventilation. *Am Rev Respir Dis* 1993;**148**:872-7.
31 O'Doherty MJ, Thomas SH, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulised aerosol to a lung model during mechanical ventilation. Effect of ventilator settings and nebuliser type, position, and volume of fill. *Am Rev Respir Dis* 1992;**146**:383-8.
32 Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulised aerosols to a lung model during mechanical ventilation. *Am Rev Respir Dis* 1993;**148**:872-7.
33 Davis JM, Russ GA, Dickerson B, Greenspan BS. Short term distribution kinetics of intratracheally administered exogenous lung surfactant. *Pediatr Res* 1992;**31**:445-50.
34 Li WZ, Chen WM, Kobayashi T. Aerosolized surfactant reverses respiratory failure in lung-lavaged rats. *Acta Anaesthesiol Scand* 1994;**38**:82-8.
35 Niven RW, Ip AY, Mittelman S, Prestrelski SJ, Arakawa T. Some factors associated with the ultrasonic nebulization of protein. *Pharm Res* 1995;**12**:53-9.
36 Boucher RMG, Kreuter J. The fundamentals of the ultrasonic atomization of medical solutions. *Ann Allergy* 1968;**26**:591-600.
37 Spragg RG, Gilliard N, Richman P, *et al*. Acute effects of a single dose of porcine surfactant on patients with adult respiratory distress syndrome. *Chest* 1994;**105**:195-202.
38 Gregory TJ, Steinberg KP, Spragg R, *et al*. Bovine surfacant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997;**155**:1309–15.