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Sequential changes in compliance and resistance after bolus administration or slow infusion of surfactant in preterm infants

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Abstract *Objective:* As bolus instillation of surfactant can lead to acute pulmonary, hemodynamic and cerebral side effects, we tested whether pulmonary mechanics and gas exchange differ between slow surfactant infusion and bolus administration. *Design and setting:* Prospective, randomized pilot study in a tertiary care university hospital. *Patients and methods:* Of 20 consecutive preterm infants (27–35 weeks' gestation) with severe respiratory distress syndrome) who were enrolled 14 with bovine surfactant finally were analyzed. *Interventions:* Six treatments were administered by slow endotracheal surfactant infusion and eight as a bolus. Static compliance (C_{stat}) and resistance (R_{rs}) were measured every 3 min. *Results:* C_{stat} first decreased and then increased in both groups. In the infusion group C_{stat} after 90 min was significantly higher than after bolus treatment but not after 15 or 45 min. R_{rs} increased about threefold, with large fluctuations in the bolus group. After 90 min PaO_2/FIO_2 had increased from 111±44 to 254±69 in the bolus group and from 86±40 to 238±102 in the infusion group, but early FIO_2 reduction and increase in PaO_2/FIO_2 seemed delayed in the infusion group. *Conclusions:* Very slow infusion of natural surfactant is at least as effective as bolus instillation in terms of improvement in C_{stat} and oxygenation after 90 min. However, until 90 min the course of C_{stat} and indices of gas exchange seem superior after bolus therapy. Because R_{rs} is substantially increased, long expiratory times are required to yield complete exhalation.

Keywords Pulmonary surfactants · Adverse effects · Lung function measurement · Respiratory distress syndrome · Infant premature · Pulmonary gas exchange

Introduction

It is widely recommended that surfactant substitution for respiratory distress syndrome (RDS) should be carried out by a single bolus administration [1]. This is an empirical practice because it is in accordance with the findings of almost all animal and patient studies. In animal studies this mode of administration has been found superior to a fractionated or infusion regimen in terms of homogeneity of surfactant distribution in the lung and improvement in oxygenation [2, 3]. However, bolus administration can lead to an obstruction of tube or tracheobronchial tree or to drug reflux [4, 5]. In addition, acute side effects on gas exchange, hemodynamics, and cerebral perfusion must be considered [6, 7, 8, 9, 10]. In contrast to surfactant, saline instillation does not produce these side effects [11]. Decrease in arterial blood pressure is associated with electroencephalographic (EEG) abnormalities and intraventricular hemorrhage (IVH) in a trial of natural surfactant [12].

The impact of respirator therapy on cerebral hemodynamics clearly depends on lung mechanics. An animal study found that introduction of positive pressure ventilation may compromise cardiac output and venous return before a drop in blood pressure occurs, but this effect is attenuated as long as lung compliance is low [13]. This may be important with respect to surfactant therapy, which should ameliorate compliance. Since the sick preterm infant lacks cerebral vascular autoregulation, fluctuations in cerebral perfusion must be avoided.

Surfactant bolus administration may have cardiovascular and pulmonary side effects, which may have a great direct or indirect impact on the neonatal brain. Some of these effects probably result from alterations in lung mechanics after surfactant bolus administration; for several reasons it has been therefore argued that a slow infusion of surfactant would be advantageous [9, 10]. However, potential advantages of a gentle administration procedure in terms of neuroprotection and avoidance of acute pulmonary complications must be weighed against the potential disadvantage of an impaired improvement in gas exchange if surfactant is not administered as a bolus.

We examined whether early kinetics (defined as a period of 90 min) of lung compliance (C_L) and resistance of the respiratory system (R_{rs}) during very slow surfactant infusion over 30–45 min differ from those after bolus administration, and how this alternative technique affects gas exchange in preterm infants with RDS.

Materials and methods

Study protocol

The study was conducted at the neonatal intensive care unit of the University Children's hospital of Münster, a tertiary care institution. Twenty consecutive preterm infants with severe neonatal respiratory failure were enrolled in this trial who had radiological and clinical signs of RDS and who should be treated with surfactant because of severely impaired gas exchange with Pa/AO_2 less than 0.15. Exclusion criteria were: congenital cardiac or pulmonary malformation, meconium aspiration, congenital sepsis and intubation with a tube of less than 3.0 mm inner diameter (ID). Three patients were excluded because they did not reach steady-state conditions with the measuring device before surfactant treatment, and three patients in the bolus group were excluded because early after treatment $tcpCO_2$ exceeded the predetermined threshold. Basic data are summarized in Table 1.

Surfactant was given according to the above criteria as part of a standard protocol of the unit and the decision was not influenced by the investigators. Endotracheal tubes were prepared with a small catheter of 0.8 mm outer diameter placed into the lumen of the tube with the tip at the distal end of the tube. The proximal end of the catheter with a Luer lock adapter was directed out of the tube connector, and the hole was sealed with silicone glue. Using a tube of at least 3.0 mm ID we found no significant increase in R_{rs} by this manipulation.

Using a list of random numbers, the patients eligible for the study were randomly assigned to receive bovine surfactant (Alveocact; Thomae, Biberach, Germany) in doses of 80–100 mg/kg body weight (volume 1.5–2.0 ml/kg b.w.) either as a bolus (n=8) or as a continuous infusion (n=6) by an electric infusion pump over 30–45 min. Variation in doses was due to a rounding process on the basis of 0.1 ml. In both groups surfactant was administered via catheter without disconnecting the patient from the ventilator. For continuous infusion the surfactant was diluted with an aliquot of saline. Patients were monitored using transcutaneous (tc) pO_2, $tcpCO_2$, and arterial oxygen saturation (SaO_2) by pulse oxymetry and heart rate by an electrocardiography monitor, and values were recorded every 3 min. Transcutaneous values were matched with at least three arterial blood gas samples before, during, and immediately after the study. FIO_2 was adjusted to keep PaO_2 between 8.6–10.0 kPa. Patients were sedated with phenobarbital or chloral hydrate as clinically indicated for mechanical ventilation, and they remained in the supine position during the whole study.

Table 1 Patients' characteristics. Values are given as range with median in parentheses. Treatment was judged successful if at 90 min FIO_2 was reduced by at least one-third of baseline FIO_2, or if PIP was reduced by at least 10%

	Bolus (n=8)	Infusion (n=6)
Gestational age (weeks)	28–32 (28.8)	27–35 (29.8)
Weight (kg)	0.91–1.5 (1.05)	0.83–2.0 (1.24)
RDS grade 3/4 (n)	5/3	4/2
FIO_2 at study entry	0.3–0.8 (0.52)	0.45–1.0 (0.64)
Treatment successful (n)	6	5

Lung function measurement

A computerized device for lung function measurement (Sensormedics 2600; Sensormedics, Yorba Linda, Calif., USA) was used to measure C_{stat} and R_{rs} with the single breath single occlusion technique. The shutter of the device was installed between the tube connector and the Y piece of the ventilator circuit and remained in place during the whole study. Patients were ventilated with two different types of continuous flow ventilators: A4-7 (Eigenbrodt, Königsmoor, Germany) or Babylog 2/Babylog 8000 (Draeger, Lübeck, Germany). Ventilation parameters were: inspiratory time 0.40–0.50 s to yield a plateau of 100 ms, frequency 35–45/min, positive end-expiratory pressure 0.4–0.65 kPa, and peak inspiratory pressure (PIP) was adjusted to yield a tidal volume of approximately 6–9 ml/kg b.w. Before surfactant administration steady-state conditions of gas exchange after insertion of the measuring device was first awaited, and baseline values of C_{stat}, R_{rs}, and transcutaneous blood gases were recorded at intervals of 3 min for at least 10 min. By gently increasing tidal volume and frequency it was attempted to compensate for the increase in dead space, which even after constructive modifications was calculated to give additional an 1.7 ml volume. If we were unable to achieve steady-state values of $tcpO_2$ or $tcpCO_2$ during 10–15 min, the study was stopped and the shutter removed.

After surfactant administration C_{stat} and R_{rs} was measured every 3 min in parallel with the other physiological parameters (see above) without disconnecting the patient from the ventilator. Also, ventilation parameters were kept constant, except for FIO_2, which was reduced liberally, and PIP was reduced, if tidal volume exceeded 10 ml/kg b.w. Short periods with $tcpCO_2$ values of up to 9.0 kPa were tolerated. If $tcpCO_2$ reached a higher level, or if oxygenation deteriorated the shutter was removed, and the patient was excluded from the study. Also, patients after hand-bagging or after any major change in ventilator settings, except for those given above, were excluded.

The study period was limited to 90 min. C_{stat} and R_{rs} at each time point (t_n) at intervals of 3 min was calculated as relative

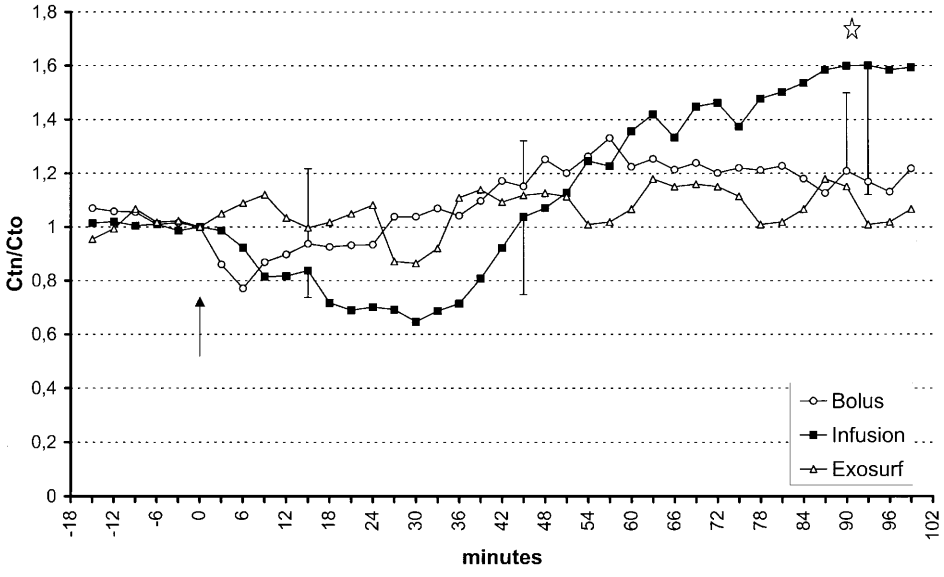

Fig. 1 Course of C_{stat} during treatment. Values are related to time point t_0, which is the last value before start of infusion or bolus administration. For clarity, SD is given for time points 15, 45, and 90 min only, and SD at 90 min is shifted to the right in the infusion group. For comparison, values from three patients treated with synthetic surfactant (Exosurf) are depicted as well. *Arrow* Surfactant administration. *$p<0.05$

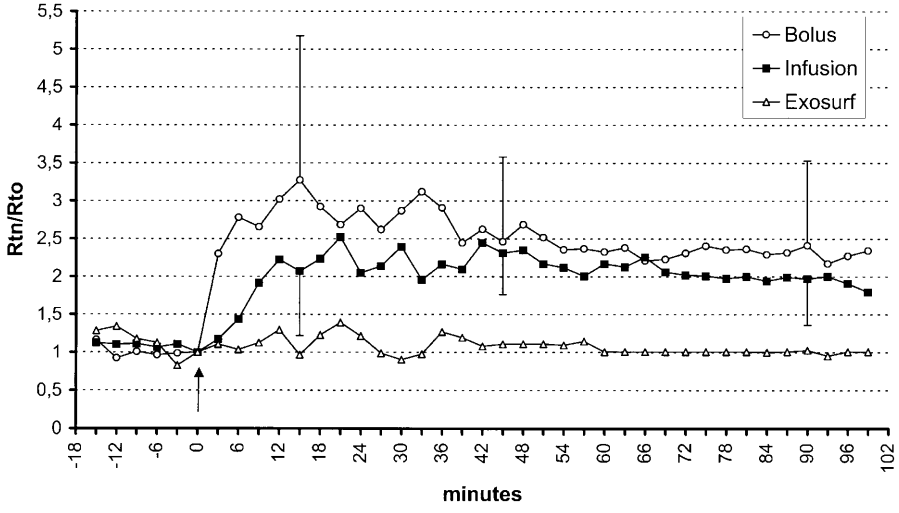

Fig. 2 Course of R_{rs} during treatment. Values are related to time point t_0, which is the last value before start of infusion or bolus administration. For clarity, SD is given for time points 15, 45, and 90 min only. For comparison, values from three patients treated with synthetic surfactant (Exosurf) are depicted as well. *Arrow* Surfactant administration

changes referring to C_{stat} or R_{rs} at t_0 (Ct_n/Ct_0 or Rt_n/Rt_0), which was the last value before start of infusion or bolus administration. Change in PaO_2/FIO_2 and FIO_2 reduction was calculated for time points 15, 45, and 90 min. Surfactant treatment was assessed successful, if at 90 min FIO_2 was reduced by at least a one-third of baseline FIO_2, or if PIP was reduced by at least 10%.

The Wilcoxon signed rank sum test was used to determine statistical significance of changes in C_{stat} and R_{rs} at 15, 45, and 90 min within each group. The Mann-Whitney test was used to test significant differences in C_{stat}, R_{rs}, FIO_2 reduction, and PaO_2/FIO_2 at 15, 45, and 90 min between the two treatment groups. Bonferroni's method was applied to correct for multiple testing, and differences were judged significant if equivalent to $p<0.05$. The slope of the regression line of PaO_2/FIO_2 increasing from t_0 to t_{90} was calculated as $\beta=(y_{t90}-y_{t0})/(x_{t90}-x_{t0})$. The study was conducted in accordance with the Helsinki regulations, and parental consent was obtained.

Results

Bolus administration was followed by a short drop in C_{stat}, which then increased. Slow infusion led to a sustained decline in C_{stat}, which returned to baseline about 45 min after the start, and at 90 min was about 60% above baseline, compared to only 20% in the bolus group. This difference between the two groups was significant ($p<0.05$), but at 15 and 45 min the Ct_n/Ct_0 values did not differ significantly between them. Comparing Ct_n/Ct_0 to baseline values, in the infusion group C_{stat} was significantly higher only at 90 min ($p<0.05$), but not at 15 and 45 min; in the bolus group differences were not significant at any of the three time points (Fig. 1).

After bolus administration R_{rs} increased to about 200% above baseline with great fluctuations from breath

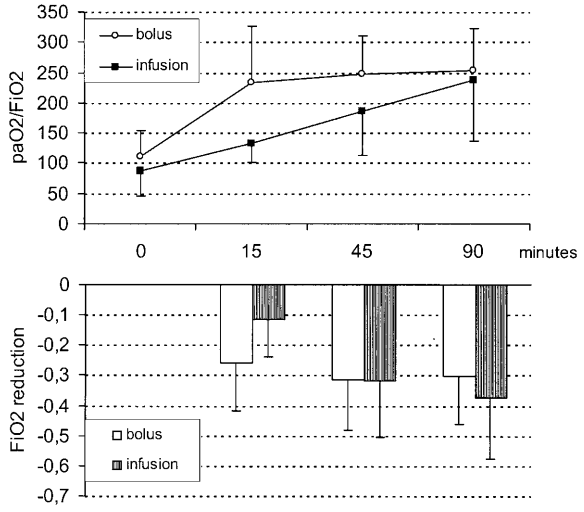

Fig. 3 Course of PaO_2/FIO_2 and FIO_2 reduction in absolute values after bolus or infusion treatment (mean ±SD)

to breath and then declined, but did not return to baseline. R_{rs} was significantly higher at 15, 45, and 90 min than at baseline ($p<0.05$). In the infusion group this effect was attenuated, and fluctuations were smaller: R_{rs} at 15, 45, and 90 min was not significantly different from baseline. Comparing the groups, differences for R_{rs} at 15, 45, and 90 min were also not significant (Fig. 2). For comparison, we also present the mean relative change in C_{stat} and R_{rs} from three infants who had received synthetic surfactant (Exosurf; Wellcome, Burgwedel, Germany) at a dose of 50–75 mg/kg body weight (volume 4–6 ml/kg b.w.) as a fractionated bolus within 5 min, as recommended by the manufacturer, and who had been studied with an identical protocol (Figs. 1, 2). In both groups the increase in C_{stat} occurred later than the increase in $tcpO_2$ or Sa_{O2}. During slow infusion it became apparent that a small part of the dose appointed for treatment was sufficient to improve oxygenation as an immediate effect.

Only at 15 min did the reduction in FIO_2 and increase in PaO_2/FIO_2 tend to be greater in the bolus group than in the infusion group, but the differences did not reach statistical significance (Fig. 3). Since baseline values for PaO_2/FIO_2 differed widely, the slope of the regression line of PaO_2/FIO_2, increasing from t_0 to t_{90}, was calculated mathematically, and the two figures were found to be comparable (bolus group 1.59 and infusion group 1.69). Six of eight treatments were successful in the bolus group versus five of six in the infusion group.

Discussion

In this study we made every effort to exclude possible confounding factors when measuring lung function in preterm infants: (a) we measured C_{stat}, which seems more reliable than dynamic compliance (C_{dyn}) [14]; (b) we measured without interrupting ventilation, because this may lead to loss of functional residual capacity; (c) significant changes in ventilator settings which might affect mechanical properties of the lung were excluded from analysis [15, 16]; (d) data were collected almost continuously before and during the whole observation time, since significant effects on gas exchange as well as side effects such as impact on cerebral perfusion also occur soon after surfactant therapy [17]. Very early continuous data on C_L, R_{rs}, and gas exchange after surfactant have not been reported previously. Several authors have noted that they measured "immediately after surfactant administration," which sometimes meant an interval of some hours, and explicitly a few minutes in only one study [18] and 0.5 h after surfactant in two further studies [17, 19].

Our finding of an initial drop of C_{stat} immediately after surfactant administration, which soon returned to baseline, is in line with that of other studies [17, 20]. However, the further course of C_{stat} or C_{dyn} has been equivocal in a number of studies. Results of several trials looking at R_{rs} after surfactant have also been equivocal. There was no change in R_{rs} 0.5 h [17, 19], 1 h [21], 3 h [22] or at different time points after administration of natural surfactant [18, 23]. After synthetic surfactant R_{rs} initially remained constant and then increased [23] or decreased, but not before 48 h [24]. There was only one single study with no more than four infants in which C_L and R_{rs} were measured at short intervals beginning immediately after administration of natural surfactant. In this study only C_{dyn} was measured, which first decreased, but the further course was not uniform, and no change in R_{rs} was noted [18]. In another small trial with calf surfactant in seven neonates conductance (which is the reciprocal of R_{rs}) was unchanged, while specific conductance (conductance per liter functional residual capacity) significantly decreased [25], but measurements began only 2 h after administration. In the study of de Winter et al. [26] porcine surfactant led to an increase in C_{stat}, but R_{rs} was unchanged; however, measurements were not made before 1.5 h after surfactant administration. In both studies an early decrease in C_{stat} and increase in R_{rs}, as demonstrated in our trial, may have been missed.

Studies reporting data on change in mechanical lung function after surfactant differ greatly with respect to a number of study conditions, but the main determinants for divergent results seem to be the use of either synthetic or natural surfactant, timing and interval of measurement, and the technique of lung function measurement (C_{stat} vs. C_{dyn} and calculation of R_{rs}). An immediate threefold increase in R_{rs} after surfactant has not been reported previously. This means acute, massive obstruction of airways, which might explain pulmonary compromise after surfactant administration, which in practice is often overcome by hand-bagging. The kinetics of C_{stat} and R_{rs} demonstrated here must be considered with respect to ventilator settings. The time constant, which is $C_L \times R_{rs}$ and gives

an important measure of the length of expiratory time needed for complete exhalation, increases 5 min after surfactant and remains high thereafter. These data may explain radiological signs of overinflation of terminal airways observed after surfactant administration. Therefore cautious corrections of ventilator settings are mandatory in this situation with a long expiratory time and an upper pressure limit set high enough to allow a spontaneous increase in PIP when inspiratory resistance increases.

In our study R_{rs} tended to be lower, and the variability from breath to breath was smaller during infusion treatment than with bolus administration. This may be an important advantage with respect to hemodynamic and cerebral effects, as well as tracheobronchial obstruction in preterm infants. A transient but significant rise in R_{rs} may lead to overinflation of the lung, which impedes venous return, and increased intrathoracic pressure is then transmitted to cerebral veins, which may occur more easily in a compliant lung after surfactant. This may be relevant for sick preterm infants, who are known to lack cerebral autoregulation, and thus are prone to IVH.

It has been argued by several authors that surfactant substitution may act as an independent risk factor for IVH [27, 28]. In addition, two recent studies of long-term outcome found that surfactant has reduced mortality, but that the rate of cerebral palsy and neurodevelopmental outcome was not changed [29, 30], and two further trials identified surfactant as a significant independent risk factor for cerebral palsy [31] and for IVH [5]. However, in meta-analyses an effect on IVH has not been confirmed. Side effects of surfactant administration on hemodynamics and cerebral function vary between surfactant types and between administration techniques. In a recent human trial altered cerebral blood flow velocity (CBFV) was more pronounced after natural than after synthetic surfactant, and was directly associated with improvement in gas exchange [32]. Following natural surfactant infants had a greater variability of CBFV and of vascular resistance index than with synthetic surfactant [33]. EEG abnormalities were also more pronounced after natural surfactant than after synthetic surfactant (Exosurf) [33], and EEG and CBFV were altered only after bolus instillation of synthetic surfactant, not after slow infusion [10]. The course of C_{stat} and R_{rs} of three patients after synthetic surfactant, presented here for comparison, confirm the findings by Pfenninger et al. [34], who also found no difference to baseline values 20 min after synthetic surfactant.

In our study, as in others, there was a significant delay between immediate improvement in oxygenation and increase in C_L. This was the case in both groups. Interestingly, the typical course of C_{stat} and R_{rs} was also observed in individual patients in whom treatment was not judged successful. To date only one study has compared improvement in gas exchange in infants who either received surfactant by bolus instillation or by a 1-min protocol via dual-lumen tube [35]. The authors reported an identical increase in Pa/AO_2 in the two groups, but in the bolus group patients were disconnected from the ventilator, which in our estimation should be avoided with respect to maintenance of functional residual capacity in a surfactant deficient lung, and therefore the bolus group may have been somewhat disadvantaged. In the instillation group the rate of bradycardia and desaturation was lower. In this respect a more protracted administration protocol, as practiced in our trial, might perhaps be even more advantageous.

An uneven distribution with a weak improvement in oxygenation after slow surfactant infusion has been reported by several authors [2, 3]. However, uneven distribution is not equivalent to impaired gas exchange [36, 37]. Surfactant nebulization as another alternative mode of surfactant administration has been shown to have several advantages over bolus administration [36, 38, 39, 40]. There are no studies on morphological distribution of surfactant after different modes of administration in human subjects.

We found that even a small amount of the surfactant dose provided in the infusion group regularly led to increased R_{rs} and decreased C_{stat}. A reduction in the cross-sectional area, as discussed by Schipper et al. [17], or acute alveolar or interstitial edema is improbable, because C_{stat} did not decrease after synthetic surfactant, nor did R_{rs} increase, even though the total volume administered intratracheally was higher in these patients than in either study group. Foaming-up is a phenomenon peculiar to natural surfactant, in contrast to synthetic surfactant. In terminal airways this may lead to trapped air, which results in reduced C_{stat} and increased R_{rs}. If bubbles resolve and surfactant forms a more homogeneous layer, C_{stat} should increase and R_{rs} decrease. It remains unclear why the course of C_{stat} differed in the two groups while the course of R_{rs} was similar. We believe that viscosity of the surfactant suspension also plays an important role for increased R_{rs}.

In conclusion, natural surfactant led to an immediate and significant increase in R_{rs}, which tended to be higher in the bolus group. C_{stat} first decreased and then increased. C_{stat} at 90 min was higher in the infusion group, but during the first 45 min C_{stat} tended to be lower than with bolus administration. Therefore expiratory time should be long enough to allow complete exhalation after surfactant. FIO_2 reduction occurred earlier in the bolus group, but after 45 min it was similar in the two groups. This trend is also reflected by the change in PaO_2/FIO_2.

The effect of different surfactant preparations on mechanical lung function, speed of improvement in gas exchange, and its potential disturbance after slow surfactant infusion should be studied in a larger trial including studies of hemodynamics and CBFV. Until then slow surfactant infusion as a potentially safer mode of surfactant administration should not be recommended as an alternative to bolus administration.

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