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A Randomized Comparison of Surfactant Dosing via a Dual-lumen Endotracheal Tube in Respiratory Distress Syndrome

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ABSTRACT. *Aim.* To determine if 1-minute instillation of Curosurf via a dual-lumen endotracheal tube without interruption of mechanical ventilation could decrease the incidence of hypoxia (drop in oxygen saturation [SaO_2] to <80%, or of transcutaneous partial pressure of oxygen [$Ptco_2$] to <50 mm Hg [6.6 kPa]) and bradycardia (heart rate below 80 beats/minute) at dosing, without affecting the efficacy of the standard bolus delivery.

Design. Prospective, multicenter, randomized, nonblinded clinical trial.

Setting. Neonatal intensive care units of the Spanish Surfactant Collaborative Group.

Patients and Methods. One hundred ninety-eight infants (birth weight 600–2000 g) with respiratory distress syndrome needing mechanical ventilation with a fraction of inspired oxygen [FIO_2] ≥0.40 were randomized before 24 hours to receive 200 mg/kg of Curosurf, either by bolus instillation (n = 99) or by a simplified dosing technique (n = 99), giving the full dose in 1 minute via a dual-lumen endotracheal tube without positioning, interruption of mechanical ventilation, or bagging. Two additional doses (100 mg/kg) were given within 12 and 24 hours of first dose, by the same method, if the infant still needed mechanical ventilation and had a FIO_2 ≥0.30. The effects of both procedures on the incidence of acute adverse events at dosing, gas exchange, ventilator requirements, and outcome at 28 days were compared.

Results. Fewer episodes of hypoxia (18 vs 40% of doses), and a smaller decrease in heart rate and SaO_2 were observed in the dual-lumen group. Efficacy of surfactant, based on improvement of oxygenation, ventilator requirements, and number of doses required, was similar in both groups. Infants in the dual-lumen group had a lower total time exposure to supplemental oxygen (195 ± 199 vs 266 ± 221 hours). No differences in the incidence of air leaks, intraventricular hemorrhage, patent ductus arteriosus, bronchopulmonary dysplasia, or survival were observed.

Conclusion. A simplified 1-minute Curosurf dosing procedure via a dual-lumen endotracheal tube without fractional doses, ventilator disconnection, changes in the infant's position, or manual bagging was found to reduce the number of dosing-related adverse transient episodes of hypoxia. Although the simplified method appeared to be as effective as bolus delivery, this should be confirmed in a larger trial. *Pediatrics* 1998;101(4). URL: http://www.pediatrics.org/cgi/content/full/101/4/e4; *Curosurf, drug administration, prematurity, pulmonary surfactant, respiratory distress syndrome.*

ABBREVIATIONS. RDS, respiratory distress syndrome; ET-tube, endotracheal tube; IMV, intermittent mechanical ventilation; FIO_2, fraction of inspired oxygen; IVH, intraventricular hemorrhage; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; a/A Po_2, arterial/alveolar Po_2 ratio; PIE, pulmonary interstitial emphysema; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

Rapid bolus tracheal instillation is the recommended dosing technique for modified surfactant preparations, and has been proven effective in the treatment of respiratory distress syndrome (RDS).[1,2] Nevertheless, it was developed empirically[3] and is difficult to standardize. Fractioning of the total dose, positional changes, interruption of mechanical ventilation, and manual bagging are usually recommended in an attempt to enhance homogeneous distribution of surfactant in the lungs,[4,5] necessary for optimal physiologic effects and efficacy.[6] Few side effects of surfactant replacement have been reported, but dosing is often accompanied by acute episodes of desaturation, bradycardia and drug reflux,[7,8] and systemic hypotension.[9,10] Sudden changes in arterial blood pressure,[10] cerebral blood flow and oxygenation,[11] and transient depression of electroencephalogram activity have also been observed.[12]

Modifications of the surfactant bolus instillation to simplify the technique and to avoid acute adverse events at dosing (eg, delivery via a dual-lumen tube[13] or a side-port adapter of the endotracheal tube (ET-tube) have been proposed,[10,14,15] and even used in a clinical trial[16] without a prospective evaluation. Because minor changes of dosing technique may have a major impact on lung distribution and efficacy,[5,17] caution has been advised before changes in the recommended delivery method are introduced into clinical practice.[18,19] In fact, only a few clinical[20,21] and experimental comparison studies[17,22–24] have been published, and they have all favored the standard bolus surfactant instillation technique.

PATIENTS AND METHODS

Study Design

Our objective was to determine if simplification of the standard Curosurf delivery procedure would decrease the incidence of

acute adverse events at dosing by 20% without affecting its clinical efficacy. We planned to recruit 97 infants to each dosing group, to detect a difference with 80% power, and a 5% level of statistical significance. The study was carried out in the neonatal intensive care units of the Spanish Surfactant Collaborative Group, and was approved by the ethics committee of each hospital. European Union guidelines for good clinical practice for trials were carefully followed. Differences in dosing procedures made blinding not feasible.

The criteria for entry were: 1) birth weight 600 to 2000 g; 2) age <24 hours; 3) clinical and radiographic evidence of RDS; 4) intermittent mechanical ventilation (IMV) with a fraction of inspired oxygen (FIO_2) ≥0.40; 5) previous placement of a dual-lumen ET-tube; and 6) parental consent. Infants with major malformations, rupture of membranes >3 weeks, Apgar score <3 at 5 minutes, or grade III-IV intraventricular hemorrhage (IVH) were excluded.

Tracheal Intubation

Only infants previously intubated with a 2.5–3.0 mm ID dual-lumen ET-tube (#5516.25 and 5516.30, Vygon, Écouen, France) were randomized. The correct position of the ET-tube was confirmed by a chest radiograph, before surfactant instillation. The characteristics of this ET-tubes are given in Fig 1.

Surfactant Treatment

A total of 198 infants were randomly assigned to one of the two groups by opening sealed opaque envelopes, sequentially numbered, and stratified by center using balanced blocks of 4 infants. All infants received initially 200 mg/kg (2.5 mL/kg) of modified porcine surfactant (Curosurf, Chiesi Farma, Parma, Italy) of known composition and effectiveness.[1] Two additional 100 mg/kg doses were given at 12 and 24 hours after the first dose, if the infant was still on IMV with a FIO_2 ≥0.30.

In the bolus dosing group, surfactant was given by rapid bolus instillation, without repositioning, as described previously.[1] Briefly, the infant was disconnected twice from the ventilator, and each half dose given via a 3.5-Fr end-hole catheter (tip located just at the lower end of the ET-tube), with the infant's head in the midline position. After each aliquot, the infant was hand-bagged for 1 minute with the same FIO_2 required before dosing, and the peak inspiratory pressure (PIP) adjusted to obtain adequate chest expansion. In the dual-lumen group, the total dose was delivered over 1 minute, via the secondary lumen of the dual-lumen ET-tube, with the infant's head in the midline position. The infant's position was not changed and IMV was not interrupted during dosing. Manual bagging was not performed but PIP was increased by 10% for 5 minutes.

In both groups, desaturation or bradycardia at dosing were managed by transiently increasing FIO_2, rate or PIP. After dosing, IMV settings were adjusted in both groups, to keep the partial pressures of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) at 50 to 70 mm Hg (6.6–9.3 kPa) and 40 to 50 mm Hg (6–7 kPa), respectively, with the lowest FIO_2 and PIP possible. Later, the FIO_2, PIP, and inspiratory to expiratory ratio were decreased as needed, and positive end-expiratory pressure (PEEP) kept at 2 to 5 cm H_2O.

Data Collection

Acute adverse events during and 5 minutes after the dosing procedures were determined by continuous monitoring of heart rate, transcutaneous oxygen saturation (SaO_2) or PO_2 ($PtcO_2$). The incidence of hypoxia (decrease in SaO_2 to <80% or of $PtcO_2$ to <50 mm Hg [6.6kPa]), bradycardia (heart rate <80 beats/minute) or both were compared. Heart rate, arterial blood pressure, ventilator settings, SaO_2 or $PtcO_2$ and arterial blood gas values were measured 5 minutes pre- and postdosing, and at fixed intervals thereafter until day 7. Arterial/alveolar PO_2 ratio (a/A PO_2) and mean airway pressure were calculated at the same time intervals, as previously described.[23] The following outcomes, as previously described,[23] were compared at day 28: pulmonary interstitial emphysema (PIE) and pulmonary hemorrhage; pneumothorax; septicemia; necrotizing enterocolitis (NEC); symptomatic patent ductus arteriosus (PDA) needing treatment; IVH; bronchopulmonary dysplasia (BPD); death; and rate of survival without BPD. The total time of exposure to supplemental oxygen and to mechanical ventilation were also compared.

Statistical Analysis

The statistical analysis was performed on an intention-to-treat basis for all eligible subjects. Evaluation of the differences between the two randomized groups was performed by independent two-tailed Student's t, Wilcoxon, Mann-Whitney U, and Fisher's exact (two-tailed) tests as appropriate. Odds ratio and the 95% confidence intervals were calculated.

RESULTS

Characterization of Patients

Ninety-nine infants were randomly assigned to each of the bolus and the dual-lumen dosing groups, and they were well-matched for birth weight, gestational age, initial FIO_2, Apgar scores at 1 and 5 minutes, gender, and use of prenatal steroids (Table 1). There were no significant differences between groups in mean baseline heart rate, arterial and airway pressure, SaO_2, PaO_2 or $PaCO_2$ (Table 2). At randomization, arterial pH, $PtcO_2$, a/A PO_2, and ventilator settings were also similar (data not shown). The median age when the first dose of surfactant was
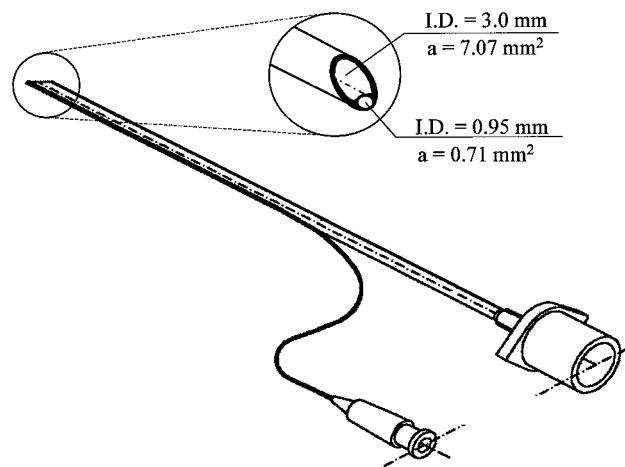
Fig 1. Schematic representation of the dual-lumen ET-tube used. Note that the distal end of the secondary lumen is located just at the tip of the main lumen of the ET-tube. The internal diameter (ID) and the internal cross-sectional area (a) of the main and secondary lumens are given. The resistance of a size 2.0-mm ID dual-lumen ET-tube, measured at two different ventilator settings (136 ± 3.9 and 132 ± 1.1 cm H_2O/L/second) were similar to those of a single-lumen ET-tube of the same size (138 ± 2.5 and 148 ± 1.6 cm H_2O/L/second). Resistance was measured (PeDs, MAS-PTI, Hatboro, PA) using a lung model (compliance = 1.0 mL/cm H_2O), and a ventilator (Bourns BP-200, Riverside, CA) at a rate of 30 cycles/minute at two different settings (PIP/PEEP = 12/2 and 25/5 cm H_2O, and peak inspiratory flow = 1.0 and 3.5 L/minute).

Within the figure:
I.D. = 3.0 mm
a = 7.07 mm²
I.D. = 0.95 mm
a = 0.71 mm²

TABLE 1. Clinical Characteristics

Groups	Dual-lumen (n = 99)	Bolus (n = 99)
Birth weight (g)	1296 ± 385	1294 ± 362
Gestational age (wk)	29.5 ± 3.0	29.6 ± 2.0
FIO_2	0.72 ± 0.2	0.75 ± 0.2
1-minute Apgar score	6 (1–9)	6 (1–9)
5-minute Apgar score	8 (3–10)	8 (2–10)
Males [No. (%)]	55 (56)	61 (62)
Prenatal steroids [No. (%)]	33 (33)	30 (30)

Values are means ±SD and median (range).
Differences are not significant.

TABLE 2.   Short-term Outcomes

Groups (Surfactant Doses)	Dual-lumen (n = 138)		Bolus (n = 155)	
	Presurfactant	Postsurfactant	Presurfactant	Postsurfactant
Heart rate (bpm)¶	149 ± 32	133 ± 23*	147 ± 16	124 ± 25§*
Mean arterial pressure (mm Hg)	43 ± 9	43 ± 8	44 ± 9	43 ± 9
Mean airway pressure (cm H_2O)	10.7 ± 3.0	10.8 ± 3.1	10.9 ± 3.1	10.9 ± 3
SaO_2 (%)	91 ± 6	95 ± 5*	90 ± 8	94 ± 6*
a/A Po_2	0.14 ± 0.08	0.36 ± 0.23*	0.15 ± 0.10	0.33 ± 0.21*
Pao_2 (mm Hg)	55 ± 23	94 ± 66*	56 ± 26	81 ± 56*
$Paco_2$ (mm Hg)	43 ± 11	45 ± 11	45 ± 11	46 ± 11

Values are mean ± SD.
* $P < .05$ comparison between 5 min presurfactant and 5 min postsurfactant values of each group (Wilcoxon test).
§ $P < .05$ comparison between groups (Student's t test), P values not significant for all other comparisons.
¶ Data indicated in the postsurfactant column is the lowest value recorded during dosing.

given was similar in both groups (8.1 ± 6.3 vs 7.3 ± 5.7 hours). In the bolus group, the total number of doses required was 155, and 53 infants needed a single dose, 36 infants received two doses, and 10 infants received three doses. In the dual-lumen group, the corresponding numbers were 138, 64, 31, and 4, respectively. These differences between groups were not statistically significant.

Short-term Adverse Effects at Dosing (Table 2 and Table 3)

Episodes of hypoxia and of hypoxia and/or bradycardia were less frequent among infants in the dual-lumen group. During dosing, the Sao_2 transiently decreased in both groups to reach minimum values of 83 ± 14 and 87 ± 10% in the bolus and dual-lumen groups, respectively ($P < .05$). The corresponding figures for $Ptco_2$ were 43 ± 1 and 47 ± 3 mm Hg (5.7 ± 1.5 and 6.3 ± 0.7 kPa, respectively; not significant). At dosing and in the 5-minute period after instillation, the observed minimum heart rate was significantly lower in the bolus group. Mean arterial pressure, $Paco_2$, and incidence of observed drug reflux were similar in both groups. The mean decrease of both heart rate and Sao_2 or $Ptco_2$ was significantly lower in the dual-lumen group.

Gas Exchange and Ventilator Settings After Surfactant Replacement

In both groups, the first dose of surfactant produced a similar sudden improvement in oxygenation, as shown by the increment in mean a/Apo_2 and Pao_2 (Table 2). Within 5 minutes of dosing, mean Fio_2 decreased significantly in both groups ($P < .05$);

from 0.75 ± 0.21 to 0.52 ± 0.23 in the bolus group, and from 0.72 ± 0.21 to 0.52 ± 0.23 in the dual-lumen group. Up to day 7, the mean a/A Po_2 and Fio_2 were comparable, and no significant differences were observed between the groups for Pao_2, $Paco_2$, or ventilator settings after surfactant treatment (data not shown).

Outcome

The rates of survival (85% vs 83%), and survival without BPD (68 vs 70%) were similar in the bolus and dual-lumen groups. No significant differences in the incidence of PIE (13% vs 9%), pneumothorax (11% vs 6%), IVH of any grade (37% vs 26%) or of grades III-IV (17% vs 11%), symptomatic PDA (48% vs 36%), or BPD (17% vs 13%) were found between the bolus and the dual-lumen groups. Furthermore, no differences were detected in the rate of septicemia, NEC, or time to extubation (data not shown). Total time on mechanical ventilation was 210 ± 199 versus 180 ± 195 hours, in the dual-lumen and bolus groups was similar. Nevertheless, total time of exposure to supplemental oxygen was significantly lower in the dual-lumen group (266 ± 221 vs 195 ± 199 hours; $P < .05$).

DISCUSSION

In this study, Curosurf given by a simplified delivery procedure (1-minute dosing via a dual-lumen tracheal tube; without fractioning, ventilator disconnection, repositioning, or bagging) produced less transient episodes of hypoxia, a smaller decrease in heart rate, and Sao_2 at dosing compared with bolus instillation. Although this study was not designed to

TABLE 3.   Short-term Results

Groups (Surfactant Doses)	Dual-lumen (n = 138)	Bolus (n = 155)	
	n (%)	n (%)	Odds Ratio (95% Confidence Interval)
Hypoxia	25 (18)	62 (40)*	0.33 (0.19–0.59)
Bradycardia	4 (3)	11 (7)	0.39 (0.09–1.36)
Hypoxia and/or bradycardia	26 (19)	65 (42)*	0.32 (0.18–0.56)
	$\bar{x}$ ± SEM	$\bar{x}$ ± SEM	Difference of Means (95% Confidence Interval)
Change in Heart rate (%)†	−8.3 ± 1.6	−15.5 ± 1.4*	−7.2 (−7.92−−6.48)
Change in Sao_2 or $Ptco_2$ (%)†	−5.9 ± 1.2	−8.9 ± 1.6*	−3 (−3.71−−2.29)

* $P < .05$.
† Mean percentage differences between basal and minimum values of heart rate and Sao_2 (or $Ptco_2$) at dosing.

evaluate long-term outcomes, it is noteworthy that the total time of exposure to supplemental oxygen was shorter in infants treated by the dual-lumen ET-tube, but survival and incidence of complications were similar in both groups.

Bolus delivery[3] is the recommended dosing method for all modified surfactants, and although effective, it was developed empirically, and might cause transient adverse events. It is also difficult to standardize, because several maneuvers are used to enhance surfactant lung distribution such as fractioning, repositioning, and manual bagging.[5,25] The real necessity of these maneuvers has been questioned, because single dosing produces a homogenous distribution,[24,26] and a good clinical response.[21] It has been suggested that the interfacial spreading capacity of surfactant may facilitate its distribution regardless of the delivery method used.[20]

Several modifications of the standard dosing method based on slow instillation and simplification of the technique have been used in clinical practice, and even in a trial comparing two surfactants,[16] without assessing if the beneficial effects of bolus instillation are preserved. In fact, only a controlled trial compared different dosing procedures requiring fractional doses with or without interruption of mechanical ventilation, and found them to be equally safe and effective.[20]

Slow infusion over 4 to 30 minutes, as used for Exosurf[8] to avoid accumulation and blockage of airways, cannot be safely used with fast-acting natural surfactants, because it produces a nonhomogeneous distribution,[17,25] and a poor physiologic response.[18] Aerosolization,[26] a form of slow delivery, although promising does not guarantee a good distribution,[25] and has yet to be proven effective in RDS. In this study, 1-minute dosing was used because it is slower than bolus delivery (10–15 seconds), yet shorter than periods shown to be ineffective in experimental[27] and clinical studies.[18] In fact, in rats with lung lavage, a 1-minute instillation of Curosurf produced similar effects on gas exchange, pulmonary mechanics, and lung distribution than bolus delivery.[24] Furthermore, in infants with RDS, a 1-minute Curosurf dosing via a side-hole in the ET-tube adapter also produced a similar immediate improvement of oxygenation, survival, and incidence of complications than if given by bolus.[21]

Bolus dosing also requires interruption of mechanical ventilation and placement of a catheter in the lumen of the ET-tube. These maneuvers might increase airway resistance, compromise gas exchange, induce alveolar derecruitment, cause desaturations,[7,8] and elevation of Paco$_2$.[15,21,28,29] To avoid the need for ventilator disconnection, surfactant dosing via a side-port in a special ET-tube adapters has been used with synthetic and natural surfactants.[20] In our previous side-hole study, the effectiveness was similar to bolus dosing, but the number of adverse events at dosing was not decreased, and a transient increase in Paco$_2$ was observed.[21]

Delivery of surfactant via the monitoring lumen of a dual-lumen ET-tube would permit infants to continue on mechanical ventilation, and thus avoid frac-

tioning, positioning, and prevent obstruction of the ET-tube. An added advantage might be the avoidance of manual bagging, which, if not properly performed, may deliver large tidal volumes that induce volutrauma.[30] The sudden increase in intrapulmonary pressure that accompanies bagging may contribute to the systemic vasodilatation and hypotension observed after surfactant dosing.[31]

Uncontrolled studies claimed slow pump infusion of Exosurf via the secondary lumen of an ET-tube causes fewer episodes of desaturation and reflux with the same effectiveness,[13] less loss of chest wall movement, and need to increase PIP.[14] To our knowledge, delivery of a modified natural surfactant via a dual-lumen ET-tube, without fractioning, repositioning, interruption of mechanical ventilation, and bagging has not been previously evaluated prospectively.

In this study, the number of episodes of desaturation was reduced by the dual-lumen infusion. Although the occurrence in 40% of bolus doses appeared to be high, it was similar to that reported with Survanta, Exosurf, or Infasurf (17–58%).[7,8,16] In our side-hole dosing study, the incidence of desaturation in the bolus group was lower (30%), but hypoxia was defined only as a Sao$_2$ <80%, whereas in this current study a drop in Ptco$_2$ to 50 mm Hg [6.6 kPa] was also included.

The occurrence of surfactant maldistribution after dosing via the dual-lumen ET-tube cannot be completely ruled out. No attempts were made to estimate distribution by chest radiograph, in view of the lack of a correlation between lung appearance and surfactant distribution measured by scintigraphy.[32] Nevertheless, this possibility seems unlikely, because of the acute improvement of gas exchange, the number of total doses, and the need for retreatment was similar in both groups. Furthermore, PIE, a complication that may accompany uneven distribution and inflation, was not increased in the dual-lumen group. The only limitation of the simplified technique was that the infants had to be previously intubated with the special dual-lumen tube. Change of ET-tube for surfactant dosing should not be undertaken, because the risks of reintubation may outweigh the advantages of this surfactant dosing technique.

In this study, Curosurf instillation via a dual-lumen tracheal tube appears to be as effective as the standard bolus delivery procedure. In fact, there was a trend toward better long-term outcomes in the dual-lumen dosing procedure. We hypothesize that these findings in relation to Curosurf delivery might also hold true for other natural surfactant preparations. As recommended, modifications of the standard bolus surfactant delivery method should not be used clinically before careful prospective evaluation.[18]

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