ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Oropharyngeal surfactant can improve initial stabilisation and reduce rescue intubation in infants born below 25 weeks of gestation

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Keywords
Delivery room intubation, Oropharyngeal surfactant, Rescue intratracheal intubation, Threshold of viability

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Received
11 May 2017; accepted 31 August 2017.

DOI:10.1111/apa.14060

ABSTRACT

Aim: Minimally aggressive and easily performed techniques that facilitate spontaneous respiratory stabilisation are required to reduce rescue intubation in extremely premature infants. This study evaluated the feasibility and safety of administering surfactant into the pharynx of infants born at <25 weeks immediately after birth.

Methods: This study of 19 infants was conducted from January 2013 to June 2014 in a tertiary perinatal centre in Prague. We administered 1.5 mL of Curosurf as a bolus into the pharynx and simultaneously performed a sustained inflation manoeuvre (SIM). The extent of the interventions, death and severe neonatal morbidity in the study group were compared with 20 controls born before the study period and 20 born after it.

Results: All infants received oropharyngeal surfactant within the median (interquartile range) time of 40 seconds (25–75) after cord camping. The surfactant had to be suctioned in one infant because of upper airway obstruction. Although more subsequent surfactant was administered in the study group, significantly fewer study period infants required intubation than the before and after controls (16% versus 75% and 58%, respectively, $p < 0.01$).

Conclusion: Oropharyngeal surfactant with simultaneous SIM was feasible and safe and reduced the need for delivery room intubation in these fragile infants.

INTRODUCTION

At the turn of the Millennium, Kattwinkel et al. (1) developed and tested the technique of prophylactic surfactant intrapartum administration without endotracheal intubation in premature infants. They found that nasopharyngeal surfactant instillation was a simple, relatively safe and potentially effective method, especially in vaginal births. Although a 2012 meta-analysis did not confirm that the prophylactic surfactant approach offered any benefits in the era of noninvasive ventilatory techniques (2), prophylaxis may have some advantages, especially in severely immature newly born infants who nearly all require exogenous surfactant. We hypothesised that surfactant instillation into the pharyngeal space and a few initial breaths would help stabilise spontaneous breathing (3,4) in infants born around the limit of viability, and this could decrease the high rate of rescue intubation (5–7). This could also decrease intraventricular haemorrhage (IVH), which is frequently associated with this difficult and stressful procedure (5,8,9). The aspiration reflex and the first few breaths were stimulated and augmented by increasing pressure on the pharynx using a simultaneously performed sustained inflation manoeuvre (SIM) (10). The infants stabilised by the administration of oropharyngeal surfactant, together with SIM, were compared with two cohorts of infants with the same gestational age who received selectively administered rescue surfactant.

Abbreviations

CPAP, Continuous positive airway pressure; FiO_2, Fraction of inspired oxygen; IVH, Intraventricular haemorrhage; PEEP, Positive end expiratory pressure; PIP, Peak inflation pressure; PPV, Positive pressure ventilation; SIM, Sustained inflation manoeuvre; SpO_2, Saturation of oxygen.

METHODS

The study was conducted in a single tertiary perinatal centre in Prague from January 2013 to June 2014. Ethical approval

Key notes

- This study evaluated the feasibility and safety of administering surfactant into the pharynx of 19 infants born at <25 weeks immediately after birth.
- It was conducted from January 2013 to June 2014 in a tertiary perinatal centre in Prague.
- Providing oropharyngeal surfactant instillation with a simultaneously sustained inflation manoeuvre was easily performed and relatively safe, even in infants born at threshold of viability and weighing from 390 to 730 g.

was given by the Ethical Committee of the General Faculty Hospital in Prague. Pregnant women with a high risk of very preterm delivery between 22 and 24 weeks of gestation were interviewed in a structured way to explain the proactive approach in detail, and informed consent was always signed before delivery. Separate informed consent describing the investigated surfactant administration was also obtained. Gestational age was primarily estimated by the obstetrician using the first- or second-trimester ultrasonography. No infant was resuscitated if they had primary asystoly. Viable infants born at 22–24 weeks of gestation without congenital anomalies, with no more than two weeks of preterm rupture of membranes and whose mothers agreed with a proactive approach, were included in the study group. In the case of multiple births, only the first infant was included and studied.

The primary outcome was the feasibility of oropharyngeal surfactant administration with simultaneously performed SIM when it was provided correctly and within the appropriate time. Safety was evaluated by the extent of ventilatory support and by the time required to reach the target values of oxygen saturation (SpO_2). The potential effectiveness was assessed by comparing the results of the study group with the two groups of infants born at 22–24 weeks of gestation and actively stabilised in the same mobile resuscitation warmer bed. The prestudy group comprised 20 infants born from January 2011 to December 2012, when SIM was not generally practised, and the poststudy group comprised 20 infants born between July 2014 and December 2015, when SIM was obligatory. The period of the study ran between those two sets of dates and comprised 19 infants (Fig. 1). The outcomes for the comparative part of the study were defined as the need for delivery room intubation, the number of SIM cases and the extent of ventilator support over three days of life and neonatal morbidity and death. The duration to achieve the target values of SpO_2 and time-related fraction of inspired oxygen (FiO_2) were also calculated and compared between all the groups.

Oropharyngeal surfactant administration and SIM

Immediately after delivery, all infants, except those born precipitously, were cord milked and placed into a specially modified mobile resuscitation warmer bed (Alfamedic sro, Lisov, Czech Republic) with two cameras attached to the frame. They immediately received 1.5 mL of Curosurf natural surfactant (80 mg/1 mL) through the mouth via a catheter inserted into the pharynx 3–4 cm from the upper lip as a rapid bolus, as demonstrated on www.https://you.tube/IP07j-hGEZg by the first author of this article (TL). SIM was simultaneously performed with a pressure of 25 cm of water for 15 seconds via an Argyle extra small size CPAP Nasal Cannula (Covidien, Mansfield, MA, USA) and was repeated twice at this maximum pressure of 25 cm H_2O if an auscultated heart rate of less than 100 beats per minute (bpm) persisted for more than 15 seconds after the end of the previous inflation. If obstruction of the upper airways was suspected, the pharynx and mouth were immediately suctioned. An increase in inflation pressure or a crossover from a T-piece to a bag and mask positive pressure ventilation (PPV) was allowed if PPV was considered insufficient for lung aeration and the heart rate did not increase.

Resuscitation procedure generally practised in all groups

The infants were stabilised and resuscitated according to the same internal standardised protocol for resuscitation of extremely low gestational age newborn infants, which is principally based on the International Liaison Committee on Resuscitation recommendations published in 2010 (11). The infants were covered with NeoWrap plastic (Fischer & Paykel Ltd, Auckland, New Zealand), and a pulse oximeter

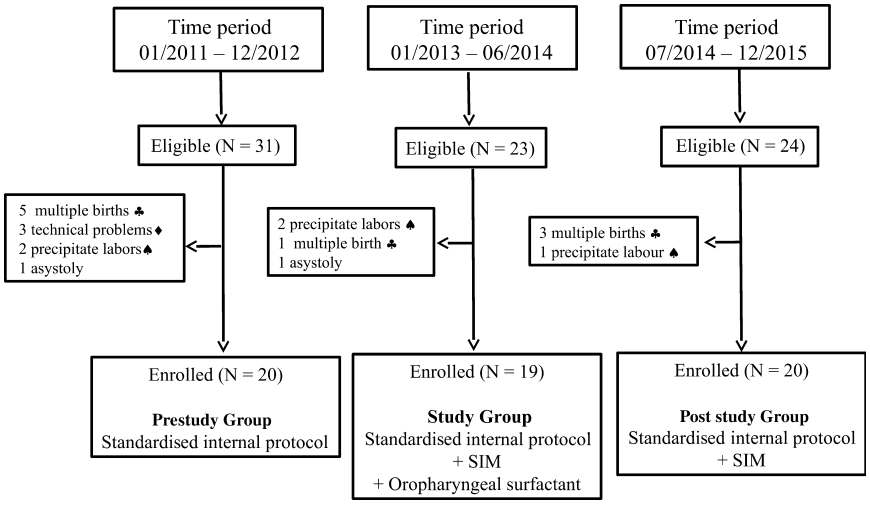

Figure 1 Diagram of group time periods and their creation. The second and/or further infant; video recording from one or both cameras were out of order; unsigned informed consent with proactive approach or with the study.

sensor was put on the right wrist as soon as possible and connected to a Masimo Radical-7 pulse oximeter (Masimo Corporation, Irvine, CA, USA). Auscultation of heart rate was the first method used to identify a bradycardic patient. Ventilatory support was exclusively provided by a Neopuff Infant T-piece Resuscitator (Fischer & Paykel Ltd), via either a soft silicone face mask, size 00 (Laerdal Medical, Stavanger, Norway), or a small or extra small rubber (Argyle CPAP Nasal Cannula; Covidien). Primary settings for the T-piece were as follows: gas flow of 10 L/minute, peak inflation pressure (PIP) of 25 cm of water and positive end expiratory pressure (PEEP) of 6 cm of water. The recommended frequency of PPV was 30–40/minute. All infants in the control groups received initial continuous positive airway pressure (CPAP) with stimulation of spontaneous breathing. PPV with PEEP in the prestudy group and SIM in poststudy group, based on the same settings and times as the study group, were initiated if bradycardia <100 bpm was recognised by auscultation or apnoea persisted for 60 seconds after cord clamping. Intubation was indicated in all infants if: (i) bradycardia without any fluctuations above 100 bpm persisted despite more than 90 seconds of PPV with PEEP, (ii) poor spontaneous breathing activity requiring PPV with PEEP was not sufficient to achieve a target range of SpO_2 and (iii) external cardiac compressions were needed. Surfactant, namely 100–200 mg/kg of Curosurf (Chiesi Farmaceutici SpA, Parma, Italy), was administered to all intubated infants in the delivery room. The FiO_2 was commenced at 0.30 and subsequently titrated in 0.10–0.20 increments every 30–60 seconds. If bradycardia of <100 bpm lasted more than 30 seconds, a switch to an FiO_2 of 1.0 was suggested and chest compressions were started. Infants who were breathing spontaneously on T-piece PEEP, or infants who had already been extubated after surfactant administration, were connected to an Infant Flow generator (CareFusion Corporation, San Diego, CA, USA) with a flow of 10–12 L/minutes and transferred to the neonatal intensive care unit (NICU). In the NICU, infants on CPAP received their first or subsequent dose of surfactant using the intubation-surfactant-extubation technique if their FiO_2 increased above 0.3. The entire vial of Curosurf (120 mg/1.5 mL) was administered independently of birth weight.

Data collection and statistical analysis

One camera recorded all the interventions, while the second camera recorded the actual time, pulse oximetry values, FiO_2, PIP and PEEP levels. Sequence analysis using TRAL 3 software (SMP Group, Zelenograd, Moscow, Russian Federation) made it possible to evaluate both of the recorded sequences on one screen at the same time. All delivery room interventions as well as FiO_2 settings, heart rate and SpO_2 values were assessed and tabulated in 15-second intervals. The time-related data were calculated from the actual SpO_2 values of each patient that was evaluated to be stable without further deterioration. The time it took to reach the values of the SpO_2 targets of more than 70%, 80% and 90% was compared with the published data reported by Dawson et al. (12). The categorical demographic and resuscitation intervention data are expressed as numbers and percentages and were compared between the groups using Pearson's chi-square or Fisher's exact test. Normally distributed noncategorical data are shown using the mean with standard deviation (SD) and skewed distributed data as medians with interquartile ranges.

RESULTS

There were 23 premature infants born between 22 + 0 and 24 + 6 weeks of gestation. One of them had primary asystoly, one was a twin, and two were delivered as a precaution and the investigational team was not available in time. Finally, surfactant was administered to 19 infants according to the protocol. The baseline characteristics are presented in Table 1. The median (IQR) end time of instillation was 40 seconds (25–75). Only three infants required intubation (16%), and the second dose of surfactant was given endotracheally in the delivery room. SIM was delivered twice to nine infants (47%) and three times to five infants (26%). The injected surfactant only was suctioned from the mouth and pharynx of one infant, 320 seconds after cord clamping, because of upper airway obstruction. No increase in PIP or crossover to bag and mask PPV were required in any infant during the stabilisation period. Nasal CPAP was given to 18 (95%) infants after their admission to the NICU. Before this, two of them required rescue intubation and were extubated immediately after intratracheal administration of surfactant in the delivery room. One infant who received rescue intubation continued on mechanical ventilation in the NICU. Subsequent surfactant was administered at a median time (IQR) of 180 minutes (128–416) in 12 (63%) infants who were primarily on CPAP. The median (IQR) FiO_2 was 0.40 (0.30–0.48) before the second dose of surfactant and 0.31 (0.26–0.33) three hours after the second dose. Six infants (32%) were mechanically ventilated at 24 hours and seven (37%) at 72 hours of life (Table 2). The median times (IQR) in seconds to reach the target SpO_2 values of more than 70%, 80% and 90% were achieved even faster in our study cohort than in more mature preterm infants who did not require any ventilatory support or oxygen: at 240 (221–318) versus 372 (216–540), 330 (270–405) versus 438 (276–608) and 435 (345–465) versus 486 (402–630), respectively.

Comparisons between the study, prestudy and poststudy groups

The need for endotracheal intubation was lowest in the study group ($p < 0.01$), and these infants were the least likely to require a third SIM ($p < 0.03$). Although 18 infants (95%) in the study group could be supported by NCPAP very early after delivery, 12 (63%) of them also required additional surfactant. The median times to reach the target values of SpO_2 of more than 70% and more than 80% were significantly shorter in the study group than in the prestudy group ($p < 0.003$), but not shorter than in the poststudy

Table 1 Baseline characteristics

	Study group N = 19	Prestudy group N = 20	Poststudy group N = 20	p Value*	p Value**
Gestational age, mean ± SD, weeks	23.9 ± 0.9	23.7 ± 0.7	23.9 ± 0.8	0.44	0.47
Birthweight, mean ± SD, g	634 ± 98	565 ± 82	575 ± 91	0.41	0.46
Any antenatal steroids, n (%)	18 (95)	15 (75)	16 (80)	0.09	0.17
Caesarean section, n (%)	4 (21)	10 (50)	11 (55)	0.06	0.03
Milking, n (%)	19 (100)	18 (90)	20 (100)	0.16	NA
Male gender, n (%)	10 (53)	11 (55)	6 (30)	0.88	0.15
Umbilical pH, mean ± SD	7.36 ± 0.07	7.31 ± 0.12	7.32 ± 0.06	0.26	0.42
Apgar score at 5 minutes, median (IQR)	7 (6; 8)	6 (5; 6.25)	7 (6; 8)	**0.01**	0.27

*Comparison between study group and prestudy group.
**Comparison between study group and poststudy group.
Bold value indicates statistical significance.

Table 2 Delivery room interventions, death and morbidity to discharge

	Study group N = 19	Prestudy group N = 20	Poststudy group N = 20	p Value*	p Value**
PPV, n (%)	19 (100)	18 (90)	20 (100)	0.16	1.0
FiO_2 1.0, n (%)	9 (47)	8 (40)	12 (60)	0.64	0.43
Endotracheal intubation, n (%)	3 (16)	15 (75)	11 (55)	**0.001**	**0.01**
Endotracheal surfactant, n (%)	3 (16)	15 (75)	11 (55)	**0.001**	**0.01**
Any SIM, n (%)	19 (100)	2 (10)	18 (90)	0.02	0.16
2nd SIM, n (%)	9 (47)	0	13 (65)	**0.001**	0.27
3rd SIM, n (%)	5 (26)	0	12 (60)	**0.01**	**0.03**
Early NCPAP, n (%)	18 (95)	12 (60)	16 (80)	**0.02**	0.17
Any surfactant, n (%)	19 (100)	18 (90)	18 (90)	0.16	0.16
Subsequent surfactant (NICU), n (%)	15 (79)	4 (20)	7 (35)	**0.01**	**0.01**
Mechanical ventilation day 1, n (%)	6 (32)	10 (50)	9 (45)	0.24	0.39
Mechanical ventilation day 3, n (%)	7 (37)	11 (55)	13 (65)	0.26	0.06
Air leaks, n (%)	1 (5)	0	0	0.30	0.30
Death, n (%)	6 (32)	7 (35)	7 (35)	0.82	0.82
Oxygen dependency at 36 weeks, n (%)	7 (37)	8 (36)	10 (50)	0.84	0.41
Death or BPD, n (%)	14 (74)	15 (75)	17 (85)	0.93	0.38
IVH gr. III–IV, n (%)	2 (11)	7 (35)	6 (30)	0.07	0.13
IVH ≥ II. grade, n (%)	4 (21)	9 (45)	9 (45)	0.07	0.07
Laparotomy, n (%)	5 (26)	4 (20)	3 (15)	0.64	0.38
ROP > II. stage, n (%)	0	1 (5)	1 (5)	1.0	1.0

PPV = positive pressure ventilation; FiO_2 = fraction of inspired oxygen; SIM = sustained inflation manoeuvre; NCPAP = nasal continuous positive airways pressure; NICU = neonatal intensive care unit; BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage; ROP = retinopathy of prematurity.
*Comparison between study group and prestudy group.
**Comparison between study group and poststudy group.
Bold value indicates statistical significance.

group, where higher median levels of FiO_2 were used (Table 3). No differences were found in the variables of short-term outcome, except for the tendency for less severe IVH in the study group.

DISCUSSION

This combined technique was feasible and easy to accomplish in all of our 19 infants, who weighed from 390 to 730 g. Of these, 16 (84%) established spontaneous breathing on CPAP within a few minutes of the surfactant being instilled, and only three infants (16%) were rescue intubated (13). The single repetition of SIM in nine infants was even less frequent than in another study, where the responses of heart rate, SpO_2 and cerebral oxygenation after SIM were studied in more mature infants (14). The median times to reach the SpO_2 targets of 70%, 80% and 90% were shorter in the study group than the reference values measured in more mature preterm infants without any pressure support or oxygen supplementation (12). The earlier achievement of a target SpO_2 of more than 70% could have been a result of quicker lung aeration after pharyngeal administration of surfactant and very early inflation pressure support in combination with some of the supplementary oxygen. These results support the potential efficacy of this technique and relative safety when hyperoxaemic peaks are avoided, with an appropriate down-regulation of FiO_2. This relatively easily performed

Table 3 Times to reach target SpO_2 and FiO_2 levels used in related times

	Study group N = 19	Prestudy group N = 20	Poststudy group N = 20	p Value*	p Value**
Time to reach SpO_2 >70%, seconds	240 (221–318)	503 (395–749)	277 (213–397)	**0.03**	0.61
FiO_2 at related time of SpO_2 >70%	0.5 (0.4–0.8)	0.4 (0.3–0.48)	1.0 (0.78–1.0)	0.12	**0.06**
Time to reach SpO_2 >80%, seconds	330 (270–405)	578 (460–767)	285 (239–427)	**0.03**	0.42
FiO_2 at related time of SpO_2 >80%	0.5 (0.4–0.6)	0.4 (0.3–0.53)	0.9 (0.4–1.0)	0.24	0.11
Time to reach SpO_2 >90%, seconds	435 (345–465)	602 (497–767)	307 (247–457)	0.14	0.29
FiO_2 at related time of SpO_2 >90%	0.4 (0.3–0.5)	0.33 (0.24–0.5)	0.75 (0.4–1.0)	0.44	0.20

Data are median (interquartile range), FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation.
*Comparison between study group and prestudy group.
**Comparison between study group and poststudy group.
Bold value indicates statistical significance.

technique, with its low rate of rescue intubation, could make this an attractive method for less skilled doctors and nurses. It is an even easier technique to perform than passing a feeding tube or a vascular catheter into the trachea, such as the technique used in less invasive surfactant administration or minimal invasive surfactant treatment (15). In a previous cohort study by Kattwinkel et al. (1), instilling nasopharyngeal surfactant before the shoulders were delivered was investigated in 22 infants born between 27 and 30 weeks of gestation. All were pressure supported by nasal CPAP of 10 cm of water from the initial breathing period. Of the 15 vaginally delivered infants, 13 were weaned to up to 30% oxygen concentration by four hours of age, with four receiving subsequent surfactant and only one developing radiologic signs of respiratory distress syndrome. Less promising results in Caesarean deliveries were speculatively explained by an insufficient squeeze of airway liquid and by taking several spontaneous breaths before surfactant could be administered. We do not know whether these potential counterproductive issues were significant in our infants. None of the four Caesarean births in our study required intubation in the delivery room, even though the mothers were under general anaesthesia in three cases. It took a median time of 40 seconds from cord clamping until the end of surfactant instillation. It is probable that a few first spontaneous breaths might occur in some infants before surfactant pharyngeal supply. We think that most of those first breaths without any pressure support were not significant enough to clear the lung liquid from the airways in such a short time, because these tiny infants have weak muscles that do not make it possible. We speculate that the surfactant could have reached the lung liquid in similar conditions, as before any first breath was taken, and that the simultaneously performed sustained inflation may have stimulated spontaneous breathing and facilitated the movement of the air and liquid interface with the surfactant layer down from the larger to the smaller airways. Despite the excellent respiratory stabilisation of most of the investigated infants, subsequent surfactant was administered to 12 (67%) infants who were primarily breathing on CPAP. However, three of them received a subsequent dose of surfactant by the intubation-surfactant-extubation technique before the criterion of FiO_2 of more than 0.30 was fulfilled. The reason for this violation was doubts expressed by the neonatologists regarding the previous unavailability of surfactant for the alveolar space after the pharynx instillation. We are not sure whether a significant amount of exogenous surfactant reaches the distal parts of lungs and, if it does, what amount would be sufficient enough for extremely immature infants whose metabolic turnover of surfactant is low. Unexpectedly, most of the infants willingly stabilised their spontaneous breathing, and the oxygen saturation targets were achieved in comfort time.

The rescue intubation rate was significantly lower in the study group than the controls, and stable SpO_2 of more than 70% was achieved in the shortest time. This occurred even though the infants were breathing lower FiO_2 than in the prestudy group, and the level was even lower in poststudy group when SIM was also used. The lowest rate of IVH in the study group could be consistent with the studies that have drawn attention to the association between delivery room intubation and a higher risk of IVH development (8,9).

Our study had a few limitations. The sample size was rather small, and the use of prestudy and poststudy controls in the comparative part of the study did not provide conclusive results. There were two differences in the study group that could have contributed to the better initial conditions of the study infants, and those were a lower rate of Caesarean deliveries and a slightly higher rate of antenatal steroids. However, we do not consider that these favourable variables were significant with regard to the study findings. Furthermore, the dose of surfactant varied between 163 and 308 mg per kilogram of body weight. We do not believe that it had a significant effect on the main outcomes, such as feasibility and safety. The potential benefits of this technique need to be further investigated in a randomised trial.

CONCLUSION

Our results confirmed that performing pharyngeal instillation of surfactant with simultaneous sustained inflation very early after delivery was a feasible and a relatively safe

technique, even for tiny infants born at <25 weeks of gestation. It may even decrease the need for rescue intubation in future cases. The impact of this surfactant prophylaxis on respiratory distress syndrome development was not yet clear. These results warrant further investigation of this technique.

FINANCE

The study was supported by OP Prague Competitiveness (project registration number CZ.2.16/3.1.00/21564).

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