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REGULAR ARTICLE

Early surfactant in spontaneously breathing with nCPAP in ELBW infants – a single centre four year experience

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Abstract

Objective: To evaluate whether the experience with a method to administer surfactant during spontaneous breathing with nasal continuous positive airway pressure (nCPAP) as primary respiratory support in infants with respiratory distress syndrome (RDS) influences the frequency of its use and affects the outcome of patients.

Methods: All inborn extremely low birthweight (ELBW) infants treated after introduction of the method were retrospectively studied (n = 196). The entire observational period was divided into four periods (periods 1–4) and compared with a control period (period 0) (n = 51). Primary respiratory support, demographics, prenatal risks and outcomes were compared.

Results: There were no changes in demographics or prenatal risks over time. The choice of nCPAP as initial airway management significantly increased from 69% to 91% and for nCPAP with surfactant from 75% to 86%. The rate of nCPAP failure decreased from 46% to 25%. Survival increased significantly between periods 0 and 1 from 76% to 90% and survival without bronchopulmonary dysplasia (BPD) rose from 65% to 80%. No changes in nonpulmonary outcomes were observed.

Conclusion: The success of nCPAP increased with increasing use of nCPAP with surfactant. Simultaneously, mortality decreased without deterioration of other outcomes indicating that the use of surfactant in spontaneous breathing with nCPAP could be beneficial.

To date, respiratory distress syndrome (RDS) still remains one of the most important causes of morbidity and mortality in extremely low birthweight (ELBW) infants. Although delivery room intubation and surfactant administration are commonly used to manage RDS, many centres are using early nasal continuous positive airway pressure (nCPAP) instead (1–6). Although data from randomized controlled trials are currently unavailable, there is growing evidence to suggest that nCPAP can improve the clinical outcomes of ELBW infants. In addition, ELBW infants also benefit from early or prophylactic surfactant administration usually related to intubation (7–9). Therefore, to combine the benefits of both principles, the so-called INSURE method (intubation surfactant extubation) was developed (10–14). However, this method needs positive pressure ventilation at least for a short time, and thereby can cause pulmonary damage and trigger pulmonary and systemic inflammation as may be assumed by some results of animal (15–17) and clinical (18) studies.

Since 1998, our centre has been using nCPAP as initial airway management. Recently, to avoid the dilemma of the choice between surfactant withholding and the risk of any mechanical ventilation (MV), we modified the INSURE procedure and developed a method to administer surfactant during spontaneously breathing with nCPAP via a thin endotracheal catheter (19). With this method surfactant is actively inspired. As safety and efficacy of a new method can change over time depending on several factors, we here report our experience of introducing and implementing this method with ELBW infants.

PATIENTS AND METHODS

Patients

During a 4-year observational period and a 11-month control period, all live-born infants with a gestational age (GA) of 23 completed weeks or more received primary neonatal care. All infants with a birthweight (BW) <1000 g and a GA between 23 and 32 full weeks were included in this retrospective analysis (n = 247). The neonatal population admitted during the 4 year observational period was divided into four quartiles in chronological order of admission (period 1: 11/16/2001 to 12/31/2002, n = 57; period 2: 1/1/2003 to 12/31/2003, n = 60; period 3: 1/1/2004 to 12/31/2004, n = 35; period 4: 1/1/2004 to 12/31/ 2004, n = 44). Management practices and outcome data over time, were conducted on infants in each quartile. The obtained data were compared to the corresponding data of a cohort of ELBW infants who were born in the 11 months before the observational period as control period (period 0, n = 51).

Study design

In our centre, a nCPAP management protocol was established 4 years before the start of the observational period and includes a strict policy for the use of nCPAP as initial airway management along with a description of the nCPAP system, guidelines for infant care on nCPAP and indicators

of nCPAP failure. Criteria for tracheal intubation and initiation of MV are also defined.

The following procedures were introduced with the nCPAP management protocol: Immediately after birth the oral cavity was suctioned and nCPAP was started by positioning a nasal mask, connected to the infant flow driver (EME, Brighton, England) set at 12 L/min, resulting in a positive endexspiratory pressure (PEEP) of 9 cm H_2O. FiO_2 was started with 0.5 and was then adjusted so that oxygen saturation measured by pulsoxymetry was 85–93%. Respiratory effort of the infants was measured using the Silverman score taken every 10 min.

If infants did not start with spontaneous breathing during the first 2 min, they were ventilated with mask and bag for 1 min. Pressure applied was controlled by manometer and limited to 25 cm H_2O. The bag was connected to a PEEP valve with a PEEP of 8 cm H_2O.

If infants did not start to breathe spontaneously within 2 min despite ventilation with mask and bag, they were intubated and subjected to MV. Infants needing a FiO_2 greater than 0.3 after establishing MV to reach a SO_2 >85% received 100 mg/kg b.w. of a natural bovine surfactant preparation (Survanta^R, Abbott, Wiesbaden, Germany).

At the end of 2001, a method to administer surfactant without intubation was defined. During the first year (period 1), the procedure was only carried out by highly experienced senior neonatologists. During this period, other physicians were trained to carry out this procedure with phantoms and nurses were trained to assist. In period 2, the newly trained physicians started to carry out the procedure themselves, and in periods 3 and 4, the procedure was used routinely.

Infants who could be managed with nCPAP after birth were eligible to receive surfactant with the new method if FiO_2 was ≥0.4 and/or the Silverman Score was ≥5 after 30 min or more. During the control period (period 0), infants fulfilling these criteria were intubated and supported with MV.

There were no changes in nursing procedures, feeding procedures or drug management during period 0–4. The attempted ranges for blood gas values remained also unchanged over time with the following target values: PaO_2 45–60 mmHg, pH >7.20 and no strict limit set for $PaCO_2$ provided the intended pH was maintained. Usually the $PaCO_2$ did not exceed 60 mmHg during the first 96 h of life. Secondary intubation or reintubation was characterized by recurrent apnoea and bradycardia not responding to stimulation or by respiratory failure with a pH persistently <7.20 or FiO_2 >0.5 for more than 2 h to maintain the PaO_2 in the intended range.

To describe clinical outcome, the mode of respiratory management in the delivery room (no support, CPAP alone, CPAP and surfactant, intubation and MV) and during the first 96 h of life were noted from the patients' records. Need for MV during the first 96 h of life in infants who had initially been managed with nCPAP was classified as failure of nCPAP as initial respiratory support. Neonatal outcome criteria such as death, BPD defined as FiO_2 >0.21 or need for any respiratory support such as MV or nCPAP at an age of 36 postmenstrual weeks, pneumothorax (PNEU), pulmonary interstitial emphysema (PIE), IVH > II° according to the classification of Papile, PVL in a sonographic screening at an age of 4 weeks after birth and/or in the sonographic screening before discharge, ROP > II+ as defined in the international classification, and NEC with Bells stage 2b or greater and need for surgical intervention were also documented.

To assess the demographic and prenatal risks, the following standardized data were collected from the patients' and their mothers' records: GA, BW, sex, Apgar score at 5 min, preterm premature rupture of membranes (PPROM) before 23 completed weeks of gestation, twin to twin transfusion syndrome according to the definition by Quintero et al. (20), use of any antenatal steroids regardless of the time interval between steroid administration and birth, small for gestational age (SGA) defined as a BW below the 10th percentile using the percentiles by Keen and Pearse (21) and early onset sepsis defined as clinical findings combined with change in neutrophil count and C-reactive protein with or without positive blood culture.

Statistical analysis

The compiled data as presented in Tables 1–4 were analysed with chi-square tests and Student's *t*-test using the SPSS

Table 1 Demographics and prenatal risks of ELBW infants in the control group (period 0) and during the observational period (periods 1–4)

	Period 0		Period 1		Period 2		Period 3		Period 4	
	All, n = 51	Survival, n = 38	All, n = 57	Survival, n = 51	All, n = 60	Survival, n = 51	All, n = 35	Survival, n = 31	All, n = 44	Survival, n = 38
Birthweight (g)	741 (175)	779 (155)	689 (182)	705 (177)	741 (167)	757 (169)	725 (183)	719 (181)	713 (180)	726 (188)
Gestational age (weeks)	26.5 (1.9)	26.9 (1.8)	26.2 (1.7)	26.3 (1.7)	26.2 (2.3)	26.4 (2.4)	25.9 (2.1)	25.9 (2.2)	25.7 (1.9)	25.9 (2.0)
Gender (male/female)	29/22	23/15	29/28	26/25	24/36	30/31	17/18	16/15	25/19	20/18
Apgar score, 5 min	7.4 (2.0)	7.7 (1.8)	7.1 (1.8)	7.3 (1.7)	7.6 (1.6)	7.8 (1.4)	7.8 (1.5)	8.0 (1.2)	7.4 (1.8)	7.8 (1.3)
PPROM <23 weeks	5	2	10	8	11	9	6	4	11	10
Early onset sepsis	14	9	14	12	17	11	12	9	17	12
Twin-to-twin transfusion	5	3	7	6	6	4	2	2	2	2
SGA <10th percentile	17	12	26	23	21	19	10	10	13	12
Any antenatal steroids	44	33	53	47	56	47	32	29	36	30

Data are given as mean and SD.

Table 2 Mortality and morbidity of survivors over time

	Period 0, n = 51 (%)	Period 1, n = 57 (%)	Period 2, n = 60 (%)	Period 3, n = 35 (%)	Period 4, n = 44 (%)
Death	13 (26)	6 (11)*	9 (15)	4 (11)	6 (14)
Morbidity of survivors					
BPD	5 (13)	5 (10)	6 (12)	2 (7)	3 (8)
PIE	5 (13)	3 (6)	2 (4)	1 (3)	3 (8)
PNEU	5 (13)	3 (6)	1 (2)	0 (0)	1 (3)
IVH >II°	7 (18)	2 (4)	5 (10)	4 (13)	2 (5)
PVL	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
ROP > II+	3 (8)	2 (4)	4 (8)	5 (16)	4 (11)
NEC	0 (0)	5 (10)	0 (0)	0 (0)	1 (3)

*$p < 0.05$ compared with period 0 using the χ^2-test.

BPD, bronchopulmonary dysplasia; PIE, pulmonary interstitial emphysema; PNEU, pheumothorax; IVH, intraventricular hemorrhage; PVL, periventricular levocomalacia; ROP, retinopathia of prematurity; NEC, necrolizing enterocolitis.

Table 3 Demographics and prenatal risks during the observational period (period 1–4) according to respiratory groups

	Group A, n = 127	Group B, n = 41	Group C, n = 26	A vs. B	A vs. C	B vs. C
Birthweight (g)	735 (176)	674 (176)	693 (177)	p = 0.06	n.s.	n.s.
Gestational age (weeks)	26.5 (2.2)	25.3 (1.5)	24.9 (1.2)	p < 0.05	p < 0.001	n.s.
Gender (male/female)	60/67	20/21	15/11	n.s.	n.s.	n.s.
Apgar score, 5 min	7.9 (1.2)	7.6 (1.3)	4.9 (1.9)	n.s.	p < 0.001	p < 0.001
PPROM <23 weeks	21	7	9	n.s.	p = 0.054	n.s.
Early onset sepsis	27	16	16	p < 0.05	p < 0.001	n.s.
Twin-to-twin transfusion	7	5	5	n.s.	p < 0.05	n.s.
SGA <10th percentile	50	15	4	n.s.	p < 0.05	n.s.

Group A: infants successfully treated with nCPAP with or without surfactant; group B: infants treated with mechanical ventilation after nCPAP failure during the first 96 h of life; group C: infants treated with mechanical ventilation after initial intubation in the delivery room; p-values >0.06 are considered to show no trend and to be not significant, they are marked with n.s.

Table 4 Mortality and morbidity during the observational period (period 1–4) according to respiratory groups

	Group A, n = 127	Group B, n = 41	Group C, n = 26	A vs. B	A vs. C	B vs. C
Death	7	6	11	n.s.	p < 0.001	p < 0.05
Morbidity of survivors						
BPD	7	4	5	p < 0.05	p < 0.05	n.s.
PIE	3	3	3	n.s.	p < 0.05	n.s.
PNEU	1	3	1	p < 0.05	n.s.	n.s.
IVH > II°	3	5	5	p < 0.05	p < 0.001	n.s.
PVL	0	0	1	n.s.	n.s.	n.s.
ROP > II+	8	3	4	n.s.	n.s.	n.s.
NEC	4	1	1	n.s.	n.s.	n.s.

Group A: infants successfully treated with nCPAP with or without surfactant; group B: infants treated with mechanical ventilation after nCPAP failure during the first 96 h of life; group C: infants treated with mechanical ventilation after initial intubation in the delivery room; p-values > 0.05 are considered to show no trend and to be not significant, they are marked with n.s.

Package, version 12.0 for MicroSoft Windows (Munich, Germany).

The Ethical Committee of the University of Cologne accepted the study as a retrospective, chart-reviewing project where all individuals are unidentified in the database.

RESULTS

A total of 247 inborn ELBW infants were admitted to the NICU from periods 0 to 4. There were no significant changes in GA, BW or any other demographic data or prenatal risks over time (Table 1).

The choice of nCPAP as initial airway management significantly increased from 69% (period 0) to 91% (period 4) ($p = 0.01$) and for nCPAP with surfactant application from 75% (period 1) to 86% (period 4) ($p = 0.21$), whereas the rate of intubation and MV due to initial respiratory illness decreased significantly from 63% (period 0) to 27% (period 4) ($p = 0.001$). Moreover, the nCPAP failure rate decreased from 46% in period 0 to 25% in period 1 ($p = 0.065$) and stayed stable over the remaining three periods, so that, in total, the number of infants who were successfully managed with nCPAP increased over time and with the increasing use of nCPAP with surfactant application.

There was no exclusionary GA for the use of nCPAP with surfactant in the delivery room. Use of nCPAP in the delivery room was higher in all GA classes after the introduction

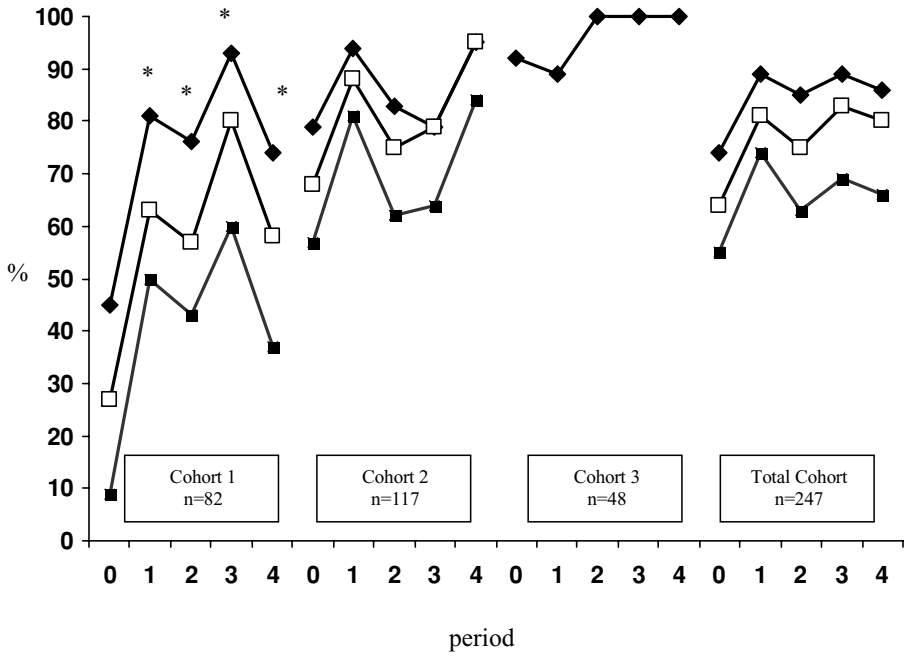

Figure 1 Development of outcome over time depending on gestational age – cohort 1: 23 0/7 to 24 6/7 weeks; cohort 2: 25 0/7 to 27 6/7 weeks; and cohort 3: ≥28 0/7 weeks. Filled rhomb: survival, open squares: survival without BPD, filled squares: survival without BPD, IVH III–IV°, PVL, ROP>II, NEC. There was no morbidity in cohort 3. *$p < 0.05$ compared with period 0 using the χ^2- test.

of surfactant application with nCPAP than in period 0. During periods 1 to 4 in all infants of 23 and 24 weeks, nCPAP was combined with surfactant administration, with an overall rate of success of 64% and 48% for 23 and 24 weeks, respectively. A total of these smallest infants of 23 and 24 weeks of 57% (40 of 70 infants) could be managed without intubation during the course of RDS in the first 96 h of live and a total of 29% (20 of 70 infants) without any intubation during the whole hospital stay.

The use of nCPAP or nCPAP with surfactant application increased continuously with increasing GA for infants of 25 weeks or more. The majority of infants with a GA of 28 weeks or less received surfactant during nCPAP using the new method; however, there was a significant drop in the frequency of surfactant application between 28 and 29 weeks from 88% to 40%. Choice of nCPAP with or without surfactant application as primary respiratory support was about 90% for all babies with a GA of 26 weeks or more. Overall need for MV during the first 96 h of life was lower or equal to 20% for all infants with a GA of 28 weeks or more.

The age at first application of surfactant decreased from period 0 to period 1 from 10.5 to 2.5 h followed by a further decrease in period 2–4 (1.1 h in period 2, 0.8 h in period 3 and 0.5 h in period 4), thus resulting in a transition from late to early rescue therapy to prophylaxis. In the subgroup of the most immature infants with a GA of 23 and 24 weeks, the age at first application was 7.9 h in period 0, 0.7 h in period 1, 0.4 h in period 2, 0.5 h in period 3 and 0.4 h in period 4. Thus, these infants got all prophylaxis during the observational period whereas they got rescue therapy during the control period.

Survival rate increased significantly between periods 0 and 1 from 76% to 90% as well as survival without BPD rising from 65% to 80%. Between periods 1 and 2, there was a slight but not significant decrease of these variables before a stable level was reached in periods 3 and 4, where survival was about 90% and survival without BPD about 80%. Overall, we observed improvement of outcome criteria over time with increased experience of staff (Table 2). However, due to the relatively low number of patients, this effect was not significant in the statistical analysis.

To assess possible effects of GA, we divided the total cohort in three cohorts: cohort 1, GA 23 0/7 to 24 6/7; cohort 2, GA 25 0/7 to 27 6/7; and cohort 3, GA ≥ 28 0/7. As Figure 1 shows the increase of survival as well as survival without BPD and survival without BPD, IVH III–IV°, PVL, ROP > II and NEC was meanly caused by an improvement of these criteria in cohort 1. For this cohort the effects were significant.

For periods 1 to 4 when nCPAP with surfactant application was available, we compared the demographic data, prenatal risks (Table 3) and the clinical outcome criteria (Table 4) of patients with successful use (group A) or failure (group B) of nCPAP with or without surfactant as well as those who had been intubated in the delivery room (group C).

Patients in groups B and C were significantly more immature than those in group A, and patients in group B also had a lower BW than patients in group C. The Apgar score

was significantly lower in group C than in groups A and B. Patients in group C were also significantly more often born after premature rupture of membranes before 23 weeks of gestation or with twin-to-twin transfusion, and were more likely to have septicemia at birth and to be not SGA.

Group A had the highest survival rate followed by group B. Group A also had the lowest rate of severe IVH and BPD with group B having a lower IVH rate than group C (Table 4).

DISCUSSION

Although there is growing evidence that the avoidance of any MV in ELBW infants is related to an improved short-term outcome (22) and that this becomes possible by using early nCPAP (3–5), the use of nCPAP as first line respiratory support still remains a point of intense discussion because there is still a not negligible rate of nCPAP failure. Therefore, many groups are looking for strategies to reduce nCPAP failure, for example by combining nCPAP with intermittent mandatory ventilation that was effective in reducing need for endotracheal intubation in infants with a GA <35 weeks (23).

But for the most immature infants at the highest risk for adverse outcome, the main point of discussion is that nCPAP is usually related to withholding of early or prophylactic surfactant that is known to be the only causal therapy of RDS (22). As early surfactant removes surfactant deficiency and early nCPAP prevents endexpiratory alveolar collapse, there are solid reasons to believe that both principles can work synergistically in the treatment of RDS.

This hypothesis is confirmed by clinical studies in that the need for MV could be significantly reduced by using a strategy where babies were intubated to receive surfactant and extubated immediately thereafter (2,10–14).

To avoid intubation and any MV, we previously developed a method to administer surfactant during spontaneous breathing with nCPAP (19). After implementing the method, we observed an increase of its use over time as well as of its success rate in terms of avoiding MV. This effect may be attributed to the growing experience of the staff. However, despite a significant reduction of mortality between period 0 and period 1 and a trend to a reduction of other adverse outcomes as IVH > II°, there was a slight deterioration of rates between periods 1 and 2 after extending the use of the method. This trend may be due to the fact that in this period attending physicians had to gain experience with the method. By periods 3 and 4, a stable level of outcome criteria was reached with death rates of 11–14% and rates of death or BPD of 17–20%.

Our observations are very similar to the reports of Aly et al. (4,5) who examined the feasibility of implementing nCPAP as the preferred form of respiratory support during the early course of RDS. They found that with growing experience the success rate increased and the outcome of treated patients (4) improved. Moreover, the authors report a decreased BPD rate over time related to increased use of nCPAP without any deterioration in nonpulmonary outcomes (4). In their study, nCPAP use increased from 11% to 67% over time for ELBW infants. In our NICU setting, the use of nCPAP was increased from 67% to 90% by combining nCPAP with surfactant administration. Aly et al. (4) report a rate of surfactant administration below 35% after implementing nCPAP and conclude that use of nCPAP as primary respiratory support could be considered as a cost saving with no associated risks. In contrast, after the introduction of our new method, we used surfactant in 90% of all ELBW infants. Finally, for the combined outcome of criteria death or BPD, we observed an incidence between 17% and 25%, whereas Aly et al. (4) report rates between 27% and 73%.

Although not primary intended, we saw a trend from rescue surfactant therapy in the control period to prophylaxis in the observational period. Therefore, it is possible that the described effects are not caused by use of the new method but by surfactant prophylaxis that is already proven to be effective in ELBW infants (7–9). On the other hand Booth et al. (14) combined prophylactic surfactant with intended early extubation to nCPAP in extremely preterm infants and they saw a remarkable number of patients (43/53, 81%), who could successfully be extubated in the first 3 days; but especially in the smallest infants below 700 g, the rate of failure of extubation and mortality were high. In contrast, we observed the main effect after introduction of our method in the cohort of the smallest infants of 23 and 24 weeks, where mortality was 26% and much lower than that reported by Booth that was 75% for these infants. However, results are not completely comparable because we treated only inborn infants, whereas Booth et al. report also about a remarkable number of outborn infants (36%).

Our observational study revealed that patients successfully treated with nCPAP with or without surfactant had the lowest morbidity and mortality compared to patients with nCPAP failure or need for ventilation immediately after birth. However, patients with nCPAP failure still showed a lower mortality than the ventilated infants. Therefore, patients secondarily ventilated after nCPAP failure seem not to have any disadvantage due to the withdrawal of primary intubation and ventilation. On the other hand, the primarily ventilated infants had a lower Apgar score after 5 min than the patients with nCPAP failure. Therefore, to which extent the poorer outcome in the group of primarily ventilated infants depends on either the poorer condition after birth or the use of MV is difficult to judge. This quandary highlights the limitation of our single centre observational study that is not adequate to form a conclusive opinion.

However, we have created a body of data including also a substantial number of infants at the limit of viability that can act as the basis to plan a prospective randomized controlled trial as it covers all essential factors including the amount of experience with the method in different NICU centres and the influence of the highest risk of the infants at the limit of viability. As the outcome of these infants in our study was at least not worse than in other studies, it seems to be justified to include these fragile infants into a prospective randomized study.

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