

Surfactant without Intubation in Preterm Infants with Respiratory Distress: First Multi-center Data

Surfactant ohne Intubation bei Frühgeborenen mit Atemnotsyndrom: Erste multizentrische Daten

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Key words

- surfactant
- respiratory distress syndrome (RDS)
- very low birth weight infant (VLBW infant)
- bronchopulmonary dysplasia (BPD)

Schlüsselwörter

- Surfactant
- Atemnotsyndrom (ANS)
- sehr kleines Frühgeborenes
- nasaler kontinuierlicher positiver Atemwegsdruck (nCPAP)
- bronchopulmonale Dysplasie (BPD)

Bibliography

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Abstract

Background: Recently in a report of a single center a method has been described to apply surfactant via a thin endotracheal catheter to very low birth weight infants spontaneously breathing with nasal continuous positive airway pressure. We now analyzed available multicenter data.

Patients and Methods: In a multicenter study investigating genetic risk factors, clinical and outcome data and data of antenatal and postnatal treatment of infants with a birth weight below 1500g were prospectively recorded. The measures of infants treated with the new method of surfactant application were compared to those of infants who received standard care. The analysis was restricted to infants with a gestational age below 31 weeks (n=1541).

Results: 319 infants were treated with the new method and 1222 with standard care. The need for mechanical ventilation during the first 72h (29% vs. 53%, p<0.001), the rate of bronchopulmonary dysplasia defined as oxygen at 36 weeks of postmenstrual age (10.9% vs. 17.5%, p=0.004) and the rate of death or bronchopulmonary dysplasia were significantly lower in the treatment group than in the standard care group. Surfactant, theophyllin, caffeine and doxapram were significantly more often and analgetics, catecholamines and dexamethasone were significantly less frequently used in the treatment group.

Conclusions: A new method of surfactant application was associated with a lower prevalence of mechanical ventilation and better pulmonary outcome. A prospective controlled trial is required to determine whether this approach is superior to standard care.

Zusammenfassung

Hintergrund: Aktuell wurde an einem einzelnen Zentrum eine Methode beschrieben, Surfactant über einen dünnen endotrachealen Katheter an sehr kleine Frühgeborene zu verabreichen, die mit Unterstützung durch einen kontinuierlichen positiven Atemwegsdruck spontan atmen. Wir analysierten jetzt verfügbare Multicenterdaten.

Patienten und Methode: In einer Multicenterstudie zur Untersuchung genetischer Risikofaktoren wurden klinische Daten, Daten zu Behandlungsergebnissen und zu vor- und nachgeburtlicher Therapie von Kindern mit einem Geburtsgewicht unter 1500g prospektiv erhoben. Die Daten der mit der neuen Methode behandelten Kinder wurden mit denen der mit Standardtherapie behandelten verglichen. Die Auswertung beschränkte sich auf Kinder mit einem Schwangerschaftsalter unter 31 Wochen (n=1541).

Ergebnisse: 319 Kinder wurden mit der neuen Methode und 1222 mit Standardtherapie behandelt. Die Häufigkeit mechanischer Beatmung während der ersten 72 Lebensstunden (29% vs. 53%, p<0,001), die einer bronchopulmonalen Dysplasie, definiert als zusätzlicher Sauerstoffbedarf nach Abschluss der 36. postmenstruellen Woche (10,9% vs. 17,5%, p=0,004) und die von Tod oder bronchopulmonaler Dysplasie lagen in der Behandlungsgruppe signifikant niedriger als in der Standardtherapiegruppe. Surfactant, Theophyllin, Koffein und Doxapram wurden signifikant häufiger und Analgetika, Katecholamine und Dexamethason signifikant seltener in der Behandlungsgruppe eingesetzt.

Schlussfolgerung: Der Einsatz der neuen Methode ging einher mit einer geringeren Notwendigkeit maschineller Beatmung und einer geringeren Rate pulmonaler Beeinträchtigung. Eine prospektive, kontrollierte Studie ist erforderlich, um eine mögliche Überlegenheit über die Standardtherapie nachzuweisen.

Introduction

▼ In very-low-birth-weight infants (VLBW infants, infants with a birth weight below 1500g) with neonatal respiratory distress syndrome (RDS) serious side effects of mechanical ventilation – like air leaks and bronchopulmonary dysplasia (BPD) – were described [3, 7]. On the other hand use of CPAP as first line therapy of RDS in VLBW infants seems to be an option to avoid mechanical ventilation [5, 15]. Early CPAP was associated with a lower incidence of BPD in many centers in Europe and the United States.

As early or prophylactic use of surfactant has been shown to reduce morbidity and mortality of infants at risk for RDS [17, 18] several procedures to administer surfactant to these infants without prolonged mechanical ventilation were reported [4, 6, 9–12, 18, 21]. None of these techniques were used in the most premature infants of less than 25 weeks gestational age. Recently, a new procedure to administer surfactant to VLBW-infants was developed and described at the Children's Hospital University of Cologne [11]. With this technique surfactant is given to spontaneously breathing VLBW-infants via a thin catheter which is placed into the trachea with a Magill-forceps under direct laryngoscopy.

After the first presentation of the new method [11] and the report of the experiences [12] we noted a rapid increase of infants treated with this "surfactant without intubation – procedure" in an observational multi-center study investigating genetic risk factors for diseases of VLBW-infants. We now report first multi-center data of VLBW-infants treated with surfactant without intubation (SWI).

Methods

▼ Patients

Our prospective, observational study analyzing genetic risk factors of VLBW-infants has been performed in Germany from September 2003 to December 2007. Infants with a birth weight below 1500g (VLBW, very-low-birth-weight), a gestational age between 24+0 and 36+6 weeks who had no lethal malformations were eligible for the study. Participating centers were allowed to report data of infants with a gestational age below 24+0 weeks, but these infants were not routinely assessed until January 2006. Written informed consent was obtained from at least one parent of each participating infant. Extensive data of antenatal and postnatal treatment and outcome data of enrolled patients were recorded by corresponding data sheets at the participating centers. In addition, we recorded basic data sets (including information about gestational age, birth weight, BPD, defined as need for supplemental oxygen at 36 weeks of postmenstrual age, blood-culture-positive sepsis, surgical procedures and death) of infants who were eligible but not included in the study because of the lack of parental consent or lethal malformation. Data quality was ensured by onsite monitoring of completed data sets every six months. After monitoring data were coded. In September 2003, nine centers participated in the study, 6 further centers were recruited until December 2007. The procedure "surfactant application without intubation" could be applied in all infants who started spontaneous breathing and was performed according to the decision of the attending neonatologist and was prospectively recorded.

Procedure

Technical details of the "surfactant without intubation procedure" have been reported in detail elsewhere [11] and are described briefly. The procedure should be performed only by physicians with expertise in endotracheal intubation. During the procedure nasal continuous positive airway pressure (nCPAP) is applied. Atropine (5 µg/kg body weight intravenously) is optional prior to the procedure. As reported in the original paper [11] the procedure was well tolerated by the infants without sedation or analgesia that are therefore not mandatory and should be limited to a dosage which does not affect spontaneous breathing. In summary, a thin catheter is placed into the trachea under direct laryngoscopy. After placement of the catheter, the laryngoscope is removed and one of the available natural surfactant preparations (Alveofact[®], Lyomark Pharma, Curosurf[®], Chiesi Pharma, Survanta[®], Abbott) in a dosage of 100 mg/kg body weight is instilled into the trachea within 1–5 min. Thereafter the catheter is removed. Close observation of the infant during the procedure is mandatory.

Ethics

All parts of the study including the "surfactant without intubation" procedure were approved by the institutional Review Board of the University of Lubeck.

Statistics

To create some hypothesis from this observational study outcome measures were compared with Fisher's exact-test and Mann-Whitney-U-test respectively, using the SPSS-Package version 16.0. for windows. All p-values are two-sided. As the study is only an observational study p-values do not confirmatively proof any of the created hypothesis.

Results

▼ Between September 2003 and December 2007 2617 VLBW infants were eligible for the study. 2028 of these infants (77.5%) were included and followed until discharge. Extensive data-sets of these infants were recorded. Information if surfactant was given without intubation (SWI) was prospectively recorded in 2005/2028 infants. Of 589 infants who were not included, basic data sets (excluding information about surfactant application without intubation) were available.

A total number of 335 infants were treated with SWI. The number of infants stratified to their gestational age is given in **Table 1**. Due to the lower incidence of respiratory distress syndrome, infants with a gestational age above 30 (weeks) + 6 (days) were rarely treated with the procedure. We therefore restricted our data analysis to 1541 infants with a gestational age of 30 weeks and below.

Clinical data of these infants are given in **Table 2**. Infants who were treated with SWI had a lower birth weight and gestational age, and were more often inborn than infants in the standard care (SC) group. Recently, we observed a rapid increase of both, the number of centers which had been using SWI (2/9 in September 2003, 12/15 in December 2007) and the percentage of infants treated with the procedure. 18/125 infants (14.4%) who were born in 2003 were treated with SWI. The numbers were 47/300 infants (15.7%) in 2004, 51/324 infants (15.7%) in 2005, 111/417 infants (26.6%) in 2006 and 92/375 infants (24.5%) in 2007, respectively. The total number of infants treated with SWI

per center was highly variable. The center in which the method was first described treated 144 infants. Other centers treated 78, 40, 15, 11, 11, 10, 5, 2 infants, and three centers treated 1 infant each.

Table 3 gives an overview of medications given to the observed infants. Due to the fact, that only 47% of the infants in the SC group received surfactant, the mean number of surfactant doses was significantly lower in the SC group (0.87 vs. 1.48 doses in the SWI group). However, this effect was only observed in infants with a gestational age above 26+0 weeks. Below this gestational age, the mean number of surfactant doses was not different between both groups (1.54 vs. 1.51 in the SWI group). Infants who received surfactant without intubation were significantly more often treated with respiratory analeptic drugs such as caffeine, theophylline and doxapram, but were less often treated with analgetics, catecholamines and dexamethasone (Table 3). Outcome data are given in Table 4. Although SWI treated infants were more immature than infants with SC, their pulmonary outcome was better. They needed less mechanical ventila-

tion (especially during the first 72 h of life) and the duration of mechanical ventilation was shorter. Moreover BPD and oxygen requirement at discharge were also significantly less frequent in infants with SWI treatment. No differences were found for other outcome parameters apart from pulmonary criteria, with the exception of intraventricular hemorrhage grade III or IV and surgical closure of patent ductus arteriosus, which were also less frequent in the SWI group.

As mentioned above the center in that the method was developed and introduced first treated 46% of all infants of the SWI group. In order to exclude that the overall outcome data is mainly influenced by center specific management effects of this hospital (and not the procedure), we analyzed our data after exclusion of all infants treated in this particular center. The results were comparable regarding ventilation during the first 72 h of life (31% vs. 54%, $p < 0.001$) and mechanical ventilation during the stay in the hospital (41% vs. 59%, $p < 0.001$), but did not reach statistical significance with respect to BPD (13% vs. 18%, $p = 0.19$). These results show the feasibility of the method in different centers with different managements.

In the SWI treated group the proportion of inborn patients and the percentage of infants treated with caffeine or theophylline was significantly higher than in the SC group. As transport might be associated with adverse outcome, and caffeine treatment is associated with a reduced rate of BPD [16], we did a multivariate logistic regression analysis with "death or BPD" as dependent variable. Variables with different frequencies between SWI- and SC-infants such as gestational age < 28 weeks, birth weight below 1000g, treatment center, transport after birth, postnatal caffeine or theophylline and SWI were included into this analysis as independent variables. After exclusion of non-predictive variables, only birth weight below 1000g (OR 4.8, 95%CI 3.2-7.3, $p < 0.001$), gestational age < 28 weeks (OR 3.4, 95%CI 2.3-5.0, $p < 0.001$), therapy with caffeine or theophylline (OR 0.4, 95%CI 0.3-0.7, $p = 0.001$) and SWI (OR 0.4, 95%CI 0.3-0.6, $p < 0.001$) were independent predictors of death or BPD.

Discussion

The use of early nCPAP can avoid mechanical ventilation in many VLBW-infants with RDS [1,2]. Early or prophylactic surfactant on the other hand has been shown to be effective in reducing

Table 1 Use of surfactant without intubation treatment and standard care stratified to gestational age.

Gestational age (weeks)	Number of infants [n]	Surfactant without intubation	
		Number of treated infants [n]	Percentage of total [%]
22	5	2	40
23	30	12	40
24	101	22	22
25	152	36	24
26	201	58	29
27	247	63	25
28	276	51	18
29	289	47	16
30	240	28	12
31	186	11	6
32	135	4	3
33	83	1	1
34	43	0	0
35	12	0	0
36	5	0	0
total	2005	335	17

Data of all VLBW infants born in the participating centers

Table 2 Clinical data of infants treated with surfactant without intubation (SWI) or standard care (SC).

	All infants n=1541	Standard care n=1222	Surfactant without intubation n=319	p*
gestational age [weeks]	27.8±1.9	27.9±1.9	27.3±1.9	<0.001
birth weight [gram]	1003±279	1018±277	945±279	<0.001
male gender [%]	53	53	51	0.4
multiple birth [%]	31	32	29	0.3
transport after birth ("Outborn") [%]	9	11	2	<0.001
antenatal steroids [%]	91	91	90	0.5
maternal origin [%]				
Germany	72	72	69	0.2
other european countries	11	11	12	0.6
Turkey, Middle East, North Africa	12	11	14	0.2
Asia	2	2	2	0.4
Sub Sahara Africa	2	3	2	0.3
other	1	1	2	0.3

Gestational age and birth weight is given as mean ± standard difference. * Fisher's exact test and Mann-Whitney U test (gestational age and birth weight) respectively. Data restricted to the patients with a gestational age < 31 weeks who were included into the genetic study

Table 3 Drugs and surfactant without intubation (SWI) or standard care (SC).

	All infants n=1 541	Standard care n=1 222	Surfactant without intubation n=319	p*
infants treated with surfactant [%]	58	47	100	<0.001
number of surfactant doses [mean±SD] all infants	0.99±1.24	0.87±1.24	1.48±1.1	<0.001
in infants below 26+0 weeks [mean±SD]	1.53±1.5	1.54±1.52	1.51±1.46	0.78
in infants above 26+0 weeks [mean±SD]	0.87±1.14	0.72±1.12	1.47±0.98	<0.001
caffeine or theophyllin [%]	90	88	98	<0.001
doxapram [%]	19	17	28	<0.001
dexamethasone [%]	6	7	2	<0.001
nitric oxide [%]	1	1	1	1.0
diuretics [%]	36	35	41	0.06
catecholamines [%]	24	27	16	<0.001
analgetics and sedatives [%]	39	40	32	0.01
antibiotics [%]	92	92	94	0.2

* Fisher's exact test and Mann-Whitney U test (number of surfactant doses) respectively

Data restricted to the patients with a gestational age <31 weeks who were included into the genetic study

Table 4 Outcome and surfactant without intubation (SWI) or standard care (SC).

	All infants n=1 541	Standard care n=1 222	Surfactant without intubation n=319	p*
mechanical ventilation during the first 72 hours of life [%]	48	53	29	<0.001
mechanical ventilation during stay in hospital [%]	55	58	42	<0.001
days on mechanical ventilation (analysis restricted to ventilated infants) [mean±SD]	16.5±24.1	17.4±25.4	11.7±14.3	0.028
bronchopulmonary dysplasia (BPD, oxygen at 36 weeks of postmenstrual age) [%]	16.1	17.5	10.9	0.004
oxygen at discharge [%]	7.2	8.3	3.2	0.001
death or BPD [%]	18.5	19.9	13.3	0.007
pneumothorax [%]	6.9	6.6	7.9	0.4
intraventricular hemorrhage grade I or II [%]	13.8	14.0	13.2	0.8
intraventricular hemorrhage grade III or IV [%]	7.9	8.7	5.0	0.035
periventricular leukomalacia [%]	4.7	4.7	4.5	1.0
sepsis with positive blood-culture [%]	21.5	21.1	22.9	0.5
ligation of persistent ductus arteriosus [%]	6.6	7.5	2.8	0.002
laser treatment of retinopathy of prematurity [%]	5.2	4.8	6.6	0.2
surgical treatment of necrotizing enterocolitis or small bowel perforation [%]	5.3	5.2	5.6	0.8
days in hospital [mean±SD]	79±34	79±36	79±28	0.5
death [%]	3.5	3.8	2.5	0.4

* Fisher's exact test and Mann-Whitney U test (days on mechanical ventilation and days in hospital) respectively

Data restricted to the patients with a gestational age <31 weeks who were included into the genetic study

mortality and morbidity in VLBW-infants [17], but is usually related to intubation and mechanical ventilation as recently discussed by Finer [8].

The present study investigated a procedure to administer surfactant that was originally described as successful approach for a cohort of patients with a gestational age below 27 weeks which also included a substantial number of patients with a gestational age below 25 weeks [11]. This observation is similar to that of Booth and coworkers [5] who tried to extubate infants at the earliest opportunity after initial positive pressure ventilation and surfactant administration and who demonstrated that even for the most premature infants management of RDS with nCPAP is safe and feasible soon after delivery with a reasonable probability of not requiring immediate reintubation.

According to some clinical and animal data [14,20,22], avoidance of any mechanical ventilation might be of utmost importance to minimize lung and brain injury. Indeed, our multicenter data suggest that SWI may have a beneficial impact at least on

the pulmonary outcome. Despite being more immature and having a lower birth weight, SWI treated infants had lower rates of mechanical ventilation, BPD and of the combined outcome criteria death or oxygen at discharge. As our study is observational, factors like demographic data, different clinical strategies or drug therapy, have to be discussed as potential confounders. Lindner and coworkers [13] recently discussed that avoidance of mechanical ventilation may be operative for changes in drug utilization. Therefore this point is of particular interest. Concerning the use of drugs, we observed great differences. In the SWI group all patients received surfactant, whereas only 47% of the SC group did so. As surfactant improves pulmonary outcome of VLBW infants [17] the observed effect might be due to surfactant itself and not to the new intervention. Furthermore, infants in the SWI group received significantly more often caffeine or theophylline. Because caffeine improves respiratory function and reduces BPD [16], their use may also have contributed to the lower incidence of BPD in the SWI group. However, the multi-

variate logistic regression analysis indicates that in our study both, caffeine and SWI, are associated with a lower rate of BPD. Due to the better pulmonary outcome, it is reasonable that less dexamethasone was administered in the SWI group. Less catecholamines were needed in the SWI group than in the SC group. This could be a consequence of the avoidance of positive pressure ventilation. On the other hand, one might argue that infants in the SWI group were less sick than infants in the SC group. Because of its observational character the study has limitations and does not allow any definitive conclusions about the superiority of the new treatment procedure. First of all it was not randomized and the indication and condition for surfactant administration were not strictly defined. Nevertheless, we have demonstrated that administration of surfactant without intubation and any mechanical ventilation is feasible in VLBW-infants with gestational ages at the limit of viability in a multicenter setting. Given the fact that experience with the method is crucial for its success [1,12], we surprisingly observed a beneficial effect of the new method in a multicenter setting where SWI was introduced during the observational period in most centers. Therefore the observational data are worth being communicated before the results of the ongoing prospective randomized controlled trials (AMV trial ISRCTN 05025922, NINSAPP trial ISRCTN 64011614) are available. Follow-up examinations are mandatory in order to prove long-term safety of the SWI procedure [19].

Conflict of interest: The authors have no conflict of interest to disclose.

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References

- 1 Aly H *et al.* Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? *Pediatrics* 2004; 114: 697-702
- 2 Ammari A *et al.* Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005; 147: 341-347
- 3 Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol.* 2002; 7 (5): 353-360
- 4 Berggren E *et al.* Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta Paediatr* 2000; 89: 460-464
- 5 Booth C *et al.* Sustainable use of continuous positive airway pressure in extremely preterm infants during the first week after delivery. *Arch Dis Child* 2006; 91: F398-402
- 6 Brimacombe J *et al.* The laryngeal mask airway for administration of surfactant in two neonates with respiratory distress syndrome. *Pediatr Anaesth* 2004; 14: 188-190
- 7 Donn SM, Sinha SK. Minimising ventilator induced lung injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; 91 (3): F226-230
- 8 Finer N. To intubate or not – that is the question: continuous positive airway pressure versus surfactant and extremely low birthweight infants. *Arch Dis Child* 2006; 91: F392-394
- 9 Jorch G *et al.* Surfactant aerosol treatment of respiratory distress syndrome in spontaneously breathing premature infants. *Pediatr Pulmonol* 1997; 24: 222-224
- 10 Kattwinkel J *et al.* Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. *J Perinatol* 2004; 24: 360-365
- 11 Kribs A *et al.* Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age ≤ 27 weeks). *Paediatr Anaesth* 2007; 17: 364-369
- 12 Kribs A *et al.* Early surfactant in spontaneously breathing with nCPAP in ELBW infants—a single centre four year experience. *Acta Paediatr* 2008; 97 (3): 293-298
- 13 Lindner U *et al.* Drug utilisation in very preterm infants: Any Changes during the past decade? *Klin Padiatr* 2008; 220: 238-242
- 14 Loeliger M *et al.* Cerebral outcomes in a preterm baboon model of early versus delayed nasal continuous positive airway pressure. *Pediatrics* 2006; 118: 1640-1653
- 15 Morley CJ *et al.* COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008; 358 (7): 700-708
- 16 Schmidt B *et al.* Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; 18: 2112-2121
- 17 Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2001; CD000510
- 18 Stevens TP *et al.* Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2004; CD003063
- 19 Strassburg HM *et al.* Long-term prognosis of former very and extremely preterm babies in adulthood in Germany. *Klin Padiatr* 2008; 220: 61-65
- 20 Thomson MA *et al.* Delayed extubation to nasal continuous positive airway pressure in the immature baboon model of bronchopulmonary dysplasia: Lung clinical and pathological findings. *Pediatrics* 2006; 118: 2038-2050
- 21 Trevisanuto D *et al.* Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. *Biol Neonate* 2005; 87: 217-220
- 22 Van Marter LJ *et al.* Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000; 105: 1194-1201