Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial

Wolfgang Göpel, Angela Kribs*, Andreas Ziegler, Reinhard Laux, Thomas Hoehn, Christian Wieg, Jens Siegel, Stefan Avenarius, Axel von der Wense, Matthias Vochem, Peter Groneck, Ursula Weller, Jens Möller, Christoph Härtel, Sebastian Haller, Bernhard Roth, Egbert Herting, on behalf of the German Neonatal Network*

Summary

Background **Surfactant is usually given to mechanically ventilated preterm infants via an endotracheal tube to treat respiratory distress syndrome. We tested a new method of surfactant application to spontaneously breathing preterm infants to avoid mechanical ventilation.**

Method **In a parallel-group, randomised controlled trial, 220 preterm infants with a gestational age between 26 and 28 weeks and a birthweight less than 1·5 kg were enrolled in 12 German neonatal intensive care units. Infants were independently randomised in a 1:1 ratio with variable block sizes, to standard treatment or intervention, and randomisation was stratified according to centre and multiple birth status. Masking was not possible. Infants were stabilised with continuous positive airway pressure and received rescue intubation if necessary. In the intervention group, infants received surfactant treatment during spontaneous breathing via a thin catheter inserted into the trachea by laryngoscopy if they needed a fraction of inspired oxygen more than 0·30. The primary endpoint was need for any mechanical ventilation, or being not ventilated but having a partial pressure of carbon dioxide more than 65 mm Hg (8·6 kPa) or a fraction of inspired oxygen more than 0·60, or both, for more than 2 h between 25 h and 72 h of age. Analysis was by intention to treat. This study is registered, number ISRCTN05025922.**

Findings **108 infants were assigned to the intervention group and 112 infants to the standard treatment group. All infants were analysed. On day 2 or 3 after birth, 30 (28%) infants in the intervention group were mechanically ventilated versus 51 (46%) in the standard treatment group (number needed to treat 6, 95% CI 3–20, absolute risk reduction 0·18, 95% CI 0·30–0·05, p=0·008). 36 (33%) infants in the intervention group were mechanically ventilated during their stay in the hospital compared with 82 (73%) in the standard treatment group (number needed to treat: 3, 95% CI 2–4, p<0·0001). The intervention group had significantly fewer median days on mechanical ventilation, (0 days. IQR 0–3 *vs* 2 days, 0–5) and a lower need for oxygen therapy at 28 days (30 infants [30%] *vs* 49 infants [45%], p=0·032) compared with the standard treatment group. We recorded no differences between groups for mortality (seven deaths in the intervention group *vs* five in the standard treatment group) and serious adverse events (21 *vs* 28).**

Interpretation **The application of surfactant via a thin catheter to spontaneously breathing preterm infants receiving continuous positive airway pressure reduces the need for mechanical ventilation.**

Funding **German Ministry of Research and Technology, University of Lübeck, and Chiesi Pharmaceuticals.**

Introduction

Continuous positive airway pressure (CPAP) and non-invasive ventilation are used in adults and children to avoid endotracheal intubation.[1–3] Preterm infants are frequently treated with surfactant for respiratory distress syndrome.[4] Surfactant is usually given via the endotracheal tube during mechanical ventilation. Therefore, preterm infants who are stabilised after birth without intubation are not treated with surfactant, which is a disadvantage of CPAP.

An approach of intubation, surfactant application during brief mechanical ventilation, and extubation before nasal CPAP has previously been used.[5–10] A meta-analysis of the use of this technique reported a reduced need for mechanical ventilation but increased surfactant use.[11] The method still requires sedation, intubation, and short mechanical ventilation, and because similar outcomes have been reported for infants treated with CPAP alone,[2,9,12] the technique of intubation, surfactant, and extubation has not been widely used.

A method of surfactant application without endotracheal intubation and mechanical ventilation has become widespread in German neonatal intensive care units. Surfactant is given to spontaneously breathing preterm infants on CPAP via a thin catheter placed in the trachea only for the time needed to give the surfactant (webvideo 1).[13,14] Observational, multicentre data suggest that this method might reduce the need for mechanical ventilation.[15] However, the safety and efficacy of this method have not been tested in a randomised controlled trial.

Lancet 2011; 378: 1627–34

Published Online September 30, 2011 DOI:10.1016/S0140-6736(11)60986-0

See Comment page 1607

*These authors contributed equally to the work

University of Lübeck, Lübeck, Germany (Prof W Göpel MD, Prof A Ziegler PhD, C Härtel MD, S Haller MD, Prof E Herting PhD); **University of Cologne, Cologne, Germany** (A Kribs MD, Prof B Roth MD); **Asklepios Klinik Barmbek, Hamburg, Germany** (R Laux MD); **University of Düsseldorf, Düsseldorf, Germany** (Prof T Hoehn MD); **Klinik für Kinder- und Jugendmedizin, Aschaffenburg, Germany** (C Wieg MD); **Kinderkrankenhaus auf der Bult, Hannover, Germany** (J Siegel MD); **University of Magdeburg, Magdeburg, Germany** (S Avenarius MD); **Altonaer Kinderkrankenhaus, Hamburg, Germany** (A von der Wense MD); **Olgahospital, Stuttgart, Germany** (M Vochem MD); **Klinik für Kinder- und Jugendliche, Leverkusen, Germany** (Prof P Groneck MD); **Evangelisches Krankenhaus, Bielefeld, Germany** (U Weller MD); **and Klinik für Kinder- und Jugendmedizin, Saarbrücken, Germany** (Prof J Möller MD)

Correspondence to: Prof Egbert Herting, Professor of Paediatrics, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany **herting@paedia.ukl.mu-luebeck.de**

See Online for webvideos 1, 2

We postulated that the application of surfactant to spontaneously breathing preterm infants would reduce the percentage of infants who subsequently need mechanical ventilation.

Methods

Study design and patients

The Avoiding Mechanical Ventilation (AMV) trial was a multicentre, randomised, controlled parallel-group study done at 12 neonatal intensive care units (level three) in Germany between October, 2007, and January, 2010. The protocol was approved by the ethics committee of each participating centre and done in accordance with good clinical practice guidelines and all applicable regulatory rules. Preterm infants with a gestational age from 26 weeks to 28 weeks plus 6 days, and with a birthweight of less than 1·5 kg were enrolled within 12 h of birth. We excluded infants with lethal malformations or those who had already been given surfactant without intubation. Infants were enrolled irrespective of their respiratory status to ensure that the sample contained the variation of the corresponding gestational-age group. Therefore, infants who were stable on CPAP without supplemental oxygen and those who were already intubated in the delivery suite were also enrolled and randomised. Because of this design, we anticipated that only 50–70% of the intervention group would receive surfactant while breathing spontaneously. We obtained written, informed, parental consent before randomisation.

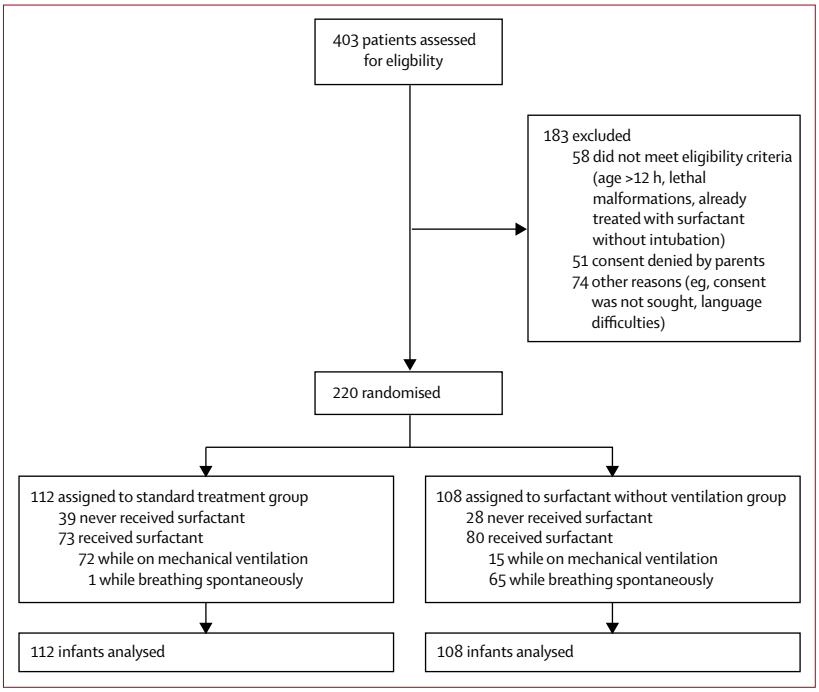

Figure 1: **Trial profile**
Infants were enrolled irrespective of their respiratory status. 15 infants in the intervention group received surfactant on mechanical ventilation, because their clinical condition after delivery required early intubation and mechanical ventilation.

Randomisation and masking

Infants in the standard treatment group were assigned to receive CPAP, rescue intubation, and surfactant treatment if needed. Those in the intervention group received the same treatment as the standard group, but if infants were stable on CPAP and a fraction of inspired oxygen (FiO_2) greater than 0·30 was needed, surfactant was given while the infant was breathing spontaneously. For multiple births all twins or triplets were assigned to the same group. The use of all three surfactant preparations licensed in Germany was allowed in this study. Infants were randomly assigned with RITA (version 1.2) in a 1:1 ratio with variable block sizes (four and six) by an independent statistician who prepared sequentially numbered, sealed, opaque envelopes stratified by centre and multiple birth status. None of the participants, those giving the interventions, those assessing outcomes, or those analysing the data were masked to the treatment.

Procedures

After birth, infants were preferentially stabilised with CPAP (≥4 cm water [H_2O]). No infant was intubated solely to give surfactant. Infants were intubated and mechanically ventilated if they had any of the following symptoms: severe respiratory distress syndrome or asphyxia requiring intubation and mechanical ventilation by judgment of the attending physician, high FiO_2 (with use of a centre-specific threshold ranging from 0·30 to 0·60), low pH (with use of a centre-specific threshold ranging from 7·15 to 7·20), or high partial pressure of carbon dioxide (pCO_2) (with use of a centre-specific threshold ranging from 60 to 70 mm Hg or 8–9·3 kPa). We encouraged physicians to extubate infants as soon as possible after successful stabilisation to minimise the time of respirator support in both groups.

For spontaneously breathing infants in the intervention group receiving nasal CPAP with an FiO_2 of more than 0·30, a thin catheter (diameter 2·5–5 french) was placed in the trachea with use of Magill forceps with direct visualisation of the vocal cords with a laryngoscope. After catheter placement, the laryngoscope was removed and surfactant (100 mg/kg bodyweight) was instilled intratracheally for 1–3 min. After instillation, the catheter was immediately removed (webvideo 1, 2). A second person observed the procedure. Sedation and analgesia were used at the discretion of each neonatologist. The use of atropine (5 µg/kg bodyweight) was optional. If apnoea occurred during the procedure, physicians were instructed to apply breaths over the CPAP system. Surfactant application without ventilation was allowed to be repeated if an FiO_2 of more than 0·40 was reached. In both groups all other treatments, including ventilator settings, adhered to local protocols.

Outcomes

The primary outcome was need for any mechanical ventilation, or being not ventilated but having pCO_2 more than 65 mm Hg (8·6 kPa) or an FiO_2 more than 0·60, or

both, for more than 2 h between 25 h and 72 h of age. Ventilation on day 1 was not included in the endpoint analysis to allow surfactant treatment in the standard treatment group. Because surfactant application in the standard treatment group is done during mechanical ventilation, all infants given surfactant in that group would automatically reach the primary endpoint if no time for extubation was allowed.

Infants with either a pCO_2 more than 65 mm Hg (8·6 kPa) or an FiO_2 more than 0·60, or both, for more than 2 h on day 2 or 3 after birth were regarded as treatment failures (ie, mechanically ventilated) to avoid the bias of withheld ventilation, because the study was not masked.

Secondary outcomes were the incidence and duration of any mechanical ventilation during the infant's time in hospital; the duration of oxygen supplementation or CPAP, or both; the number of surfactant doses given per infant; bronchopulmonary dysplasia;[16] death or bronchopulmonary dysplasia; death or treatment with supplemental oxygen at discharge; FiO_2 and oxygen saturation in the first 3 days after birth; drug treatments given (sedatives and analgesics, inotropes, methylxanthines, diuretics, and dexamethasone); and serious adverse events (eg, pneumothorax, intraventricular haemorrhage grade 3 or 4, pulmonary haemorrhage, periventricular leukomalacia, surgical treatment of patent ductus arteriosus, surgical treatment of necrotising enterocolitis or focal intestinal perforation, laser therapy or cryotherapy of retinopathy, and death).

Statistical analysis

We estimated that 60% of infants in the standard treatment group and 40% in the intervention group would need mechanical ventilation on day 2 or 3 after birth on the basis of data from our previous observational study.[15] To prove our hypothesis, we used a two-tailed exact test of Fisher to calculate that 105 infants per group would be needed, for a significance of 0·05, and a power of 80%.

The analysis was done according to the intention-to-treat principle. The two-sided exact test of Fisher was used to compare the main dichotomous outcomes. The absolute risk reduction and the number needed to treat together with 95% CIs and the relative risk (RR) were calculated as effect measures. Two sensitivity analyses that adjusted for stratified enrolment of multiple births were done to confirm the robustness of the primary outcome analysis.[17,18] The Mann-Whitney U test was used to compare continuous outcome variables such as the duration of mechanical ventilation. Analyses were done with SPSS (version 17.0) and StatXact 8 (version 8).

This study is registered, number ISRCTN05025922.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

	Intervention group (n=108)	Standard treatment group (n=112)
Gestational age (weeks)	27·6 (0·8)	27·5 (0·8)
Birthweight (g)	975 (244)	938 (205)
Mean cord blood arterial pH	7·34 (0·07)	7·34 (0·08)
Postnatal CO_2 (mm Hg)	55 (13)*	53 (12)†
First recorded FiO_2	0·32 (0·14)	0·33 (0·18)
Boys	53 (49%)	58 (52%)
Multiple births	37 (34%)	35 (31%)
Use of antenatal steroids	104 (96%)	107 (96%)
Caesarean section	101 (94%)	104 (93%)
Outborn	0	1 (1%)

Data are mean (SD) or number (%). CO_2=carbon dioxide. FiO_2=fraction of inspired oxygen. *7·3 kPa (1·7). †7·1 kPa (1·6).

Table 1: **Patients' baseline clinical characteristics**

	Intervention group (n=108)	Standard treatment group (n=112)	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)	p value*
All infants (%)	30 (28%)	51 (46%)	–0·18 (–0·30 to –0·05)	6 (3 to 20)	0·008
26 weeks' gestation (%)	11/26 (42%)	11/26 (42%)	0·00 (–0·27 to 0·27)	..	1·000
27 weeks' gestation (%)	12/41 (29%)	21/44 (48%)	–0·18 (–0·39 to 0·03)	..	0·119
28 weeks' gestation (%)	7/41 (17%)	19/42 (45%)	–0·28 (–0·47 to –0·08)	4 (2 to 13)	0·009

The primary outcome was any mechanical ventilation, or being not ventilated but having a partial pressure of carbon dioxide more than 65 mm Hg (8·6 kPa) or a fraction of inspired oxygen more than 0·60, or both, for more than 2 h between 25 h and 72 h of age. Data are n (%) or n/N (%), unless otherwise stated. *Calculated with Fisher's exact test.

Table 2: **Primary outcome**

Results

Figure 1 shows the trial profile. Between Oct, 8, 2007, and Aug 1, 2009, 403 infants were eligible for the study in 12 centres. 220 infants (55%) were enrolled and analysed (figure 1). No significant differences were reported between included and excluded infant's birthweight, gestational age, bronchopulmonary dysplasia or death (data not shown). The trial was completed as planned; the last patient was discharged in January, 2010. 112 infants were randomly assigned to receive standard treatment and 108 were randomly assigned to the surfactant without ventilation group. 39 infants in the standard treatment (35%) and 28 infants in the intervention group (26%) never received surfactant. Surfactant was given without ventilation to 65 infants (60%) in the intervention group and inadvertently to one infant (1%) in the standard treatment group. This participant was analysed as a member of the standard treatment group (figure 1) in line with the intention-to-treat principle. Clinical characteristics were similar at randomisation (table 1).

	Intervention group (n=108)	Standard treatment group (n=112)	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)	p value
Any mechanical ventilation					
All infants (%)	36 (33%)	82 (73%)	−0·40 (−0·52 to −0·27)	3 (2 to 4)	<0·0001
26 weeks' gestation (%)	11/26 (42%)	19/26 (73%)	−0·31 (−0·55 to −0·29)	4 (2 to 34)	0·048
27 weeks' gestation (%)	18/41 (44%)	33/44 (75%)	−0·31 (−0·50 to −0·08)	4 (2 to 12)	0·004
28 weeks' gestation (%)	7/41 (17%)	30/42 (71%)	−0·54 (−0·71 to −0·34)	2 (2 to 3)	<0·0001
Other pulmonary outcomes					
Duration of mechanical ventilation (days)	0 (0–3)	2 (0–5)	..	..	<0·0001
Any respiratory support (mechanical ventilation or CPAP) (days)	25 (11–38)	29 (16–41)	..	..	0·069
Supplemental O_2 (days)	5 (2–32)	19 (2–42)	..	..	0·059
Pulmonary haemorrhage	1 (1%)	3 (3%)	..	..	0·622
Pneumothorax	4 (4%)	8 (7%)	..	..	0·375
Supplemental O_2 at age 28 days*	30 (30%)	49 (45%)	..	..	0·032
Death or supplemental O_2 at 28 days	37 (34%)	52 (46%)	..	..	0·075
Bronchopulmonary dysplasia at 36 weeks postmenstrual age*	8 (8 %)	14 (13%)	..	..	0·268
Discharged home, treated with O_2	1 (1%)	1 (1%)	..	..	1·000
Death or bronchopulmonary dysplasia at 36 weeks postmenstrual age	15 (14%)	17 (15%)	..	..	0·850
Oxygen saturation (%)					
Day 1	93% (91–96)	93% (91–96)	..	..	0·339
Day 2	93% (91–96)	94% (92–96)	..	..	0·299
Day 3	95% (92–97)	95% (92–97)	..	..	0·907
FiO_2					
Day 1	0·25 (0·22–0·29)	0·24 (0·21–0·30)	..	..	0·901
Day 2	0·22 (0·21–0·28)	0·22 (0·21–0·27)	..	..	0·973
Day 3	0·21 (0·21–0·23)	0·21 (0·21–0·25)	..	..	0·857

Data are n (%), n/N (%), or median (IQR) unless otherwise stated. O_2=oxygen. CPAP=continuous positive airway pressure. FiO_2=fraction of inspired oxygen. *Data restricted to infants who were alive (intervention group n=101, standard treatment group n=109).

Table 3: **Secondary outcomes—pulmonary outcomes**

More infants in the standard treatment group than in the intervention group were mechanically ventilated on day 2 or 3 after birth (RR 0·70, 95% CI 0·54–0·90; table 2). The largest differences occurred at 28 weeks' gestation (tables 1, 2). None of the spontaneously breathing infants exceeded the predefined CO_2 or FiO_2 limits for more than 2 h on day 2 or 3 after birth (data not shown). Adjustment for multiple birth did not change the significant difference of the primary endpoint (data not shown).

The number of infants who received any mechanical ventilation during the stay in the hospital was lower in the intervention group than in the standard treatment group (RR 0·42, 95% CI 0·31–0·59; table 3). This difference is attributable to the large proportion of infants in the intervention group who were managed exclusively with CPAP after surfactant application without intubation. 65 (60%) infants in the intervention group were treated with surfactant while breathing spontaneously. 13 of 65 infants (20%) were mechanically ventilated on day 2 or 3 after birth and reached the primary endpoint. 17 of 65 infants (26%) were mechanically ventilated at any time during their stay in the hospital, and 48 of 65 (74%) received only CPAP (webappendix p 1). Figure 2 shows the number of infants who were never intubated during the first 28 days after birth. In both groups most infants were intubated between days 1 and 4 after birth (figure 2).

See Online for webappendix

Because intubation during the first hour after birth and during the randomisation period (the first 12 h after birth) might be due to complications other than early respiratory distress syndrome (eg, perinatal asphyxia), we did two secondary analyses of all infants who received CPAP during the first hour and at 12 h after birth (webappendix pp 2–3). 1 h after birth, 97 of 108 (90%) infants in the intervention group and 83 of 112 (74%) in the standard treatment group were stabilised on CPAP alone. In this subgroup, the difference between the intervention and standard treatment groups was even greater than in the primary analysis. 21 of 97 (22%) infants in the intervention group received mechanical ventilation on day 2 or 3 after birth compared with 36 of 83 infants (43%) in the standard treatment group (p=0·002, Fisher's exact test).

Participating centres were encouraged to extubate infants as soon as possible. Of 81 infants who were intubated on the first day after birth, 27 (33%) were extubated within the first 24 h. Figure 2 shows the proportion of infants who received mechanical ventilation during the first 28 days after birth. The total number of ventilation days was 599 (range 0–51) in the standard

treatment group versus 242 days (range 0–24) in the intervention group (table 3).

Figure 2 shows the proportion of infants who received supplemental oxygen within 28 days of birth. Supplemental oxygen on day 28 was given to more infants in the standard treatment group than in the intervention group (RR 0·73, 95% CI 0·57–0·95; table 3). This difference was not significant when oxygen treatment was analysed at 36 weeks' postmenstrual age (table 3). Oxygen saturation and FiO_2 during the first 3 days after birth did not differ significantly between the standard treatment and intervention groups (table 3). We detected no significant differences in mean number of surfactant doses per infant and the percentage of infants treated with surfactant (table 4). Infants in the intervention group were treated earlier than were those infants in the standard treatment group (table 4).

The first attempt to replace surfactant during spontaneous breathing was not successful in three out of 65 (5%) infants. The second attempt to apply surfactant was successful in all of these infants. Infants who received surfactant replacement during spontaneous breathing had slightly lower minimum heart rates and oxygen saturations (SpO_2) than did those who did not, but this finding was borderline significant (table 4). Four infants in the intervention group had heart rates lower than 100 beats per min, (range 78–90). The lowest SpO_2 readings during surfactant replacement in these four infants were between 67% and 85%. Infants in the intervention group were less frequently treated with analgesics and sedatives than were those in the standard treatment group, because of the low treatment rate of infants who were given surfactant while breathing spontaneously (table 4, webappendix p 1). However, the higher analgesic and sedative treatment rates in the standard treatment group than in the intervention group did not affect the primary endpoint (webappendix p 3). We recorded no significant differences between use of other drugs or incidence of serious adverse events (table 4). 12 infants died (table 4). None of the deaths or other adverse events were related to the application of surfactant.

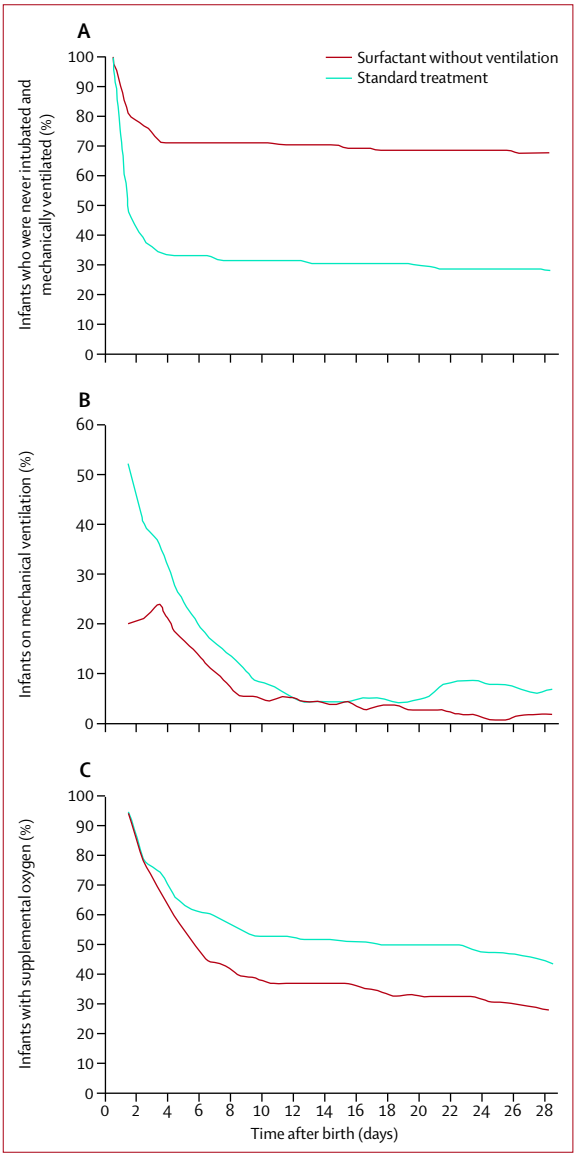

Figure 2: **Proportion of infants who receive no intubation (A), mechanical ventilation (B), and supplemental oxygen (C) during the first 28 days after birth**

Discussion

Findings from this study have shown that the application of surfactant to spontaneously breathing preterm infants is feasible and reduces the need for subsequent mechanical ventilation. This effect was apparent in our primary analysis, which was designed to account for the variability of each gestational age group, but was even more pronounced in the subgroup of infants who were stabilised with CPAP after birth.

Infants with established respiratory distress syndrome who received animal-derived surfactant treatment in controlled trials done in the 1980s and 1990s had a decreased mortality, and an increased chance of survival without chronic lung disease.[4] In 1992, Verder and colleagues[19] reported some cases of surfactant given to spontaneously breathing preterm infants via a thin catheter. No further information about this method was published, until it became popular again in the late 2000s.[13–15,20] Retrospective, multicentre data suggest that the application of surfactant to spontaneously breathing infants is associated with low rates of mechanical ventilation, bronchopulmonary dysplasia, and death or bronchopulmonary dysplasia .[15] Our findings lend support to the hypothesis that surfactant treatment of spontaneously breathing patients is safe and effectively reduces the need for mechanical ventilation (panel).

Since mechanical ventilation might cause lung injury in preterm infants, several other approaches to avoid mechanical ventilation have been studied.[21,22] The

	Intervention group (n=108)	Standard treatment group (n=112)	p value
Drug treatments			
Analgesics and sedatives	28 (26%)	46 (41%)	0·022
Inotropes	18 (17%)	20 (18%)	0·860
Methylxanthines	102 (94%)	110 (98%)	0·165
Diuretics	41 (38%)	47 (42%)	0·583
Dexamethasone	1 (1%)	3 (3%)	0·622
Serious adverse events			
Any	21 (19%)	28 (25%)	0·336
Grade 3 or 4 intraventricular haemorrhage	8 (7%)	6 (5 %)	0·590
Cystic periventricular leukomalacia	5 (5%)	2 (2%)	0·274
Surgical treatment of necrotising enterocolitis or focal intestinal perforation	3 (3%)	4 (4%)	1·000
Laser or cryotherapy of retinopathy of prematurity	3 (3%)	1 (1%)	0·363
Surgical treatment of patent ductus arteriosus	0	2 (2%)	0·498
Death	7 (7%)	5 (5%)	0·564
Have specified adverse events*	16 (15%)	16 (14%)	1·000
Have other specified events†	5 (5%)	12 (11%)	0·129
Surfactant treatment			
Infants treated with surfactant	80 (74%)	73 (65%)	0·187
Surfactant preparation‡	..	..	..
Poractant alfa	65 (81 %)	57 (78 %)	..
Beractant	14 (18 %)	14 (19%)	..
Bovactant	1 (1%)	2 (3 %)	..
Surfactant doses per infant	1 (0–2)	1 (0–1)	0·195
FiO_2 at first surfactant treatment§	0·40 (0·35–0·55)	0·45 (0·40–0·60)	0·056
Time until first surfactant treatment after birth (min)‡	55 (18–145)	135 (45–658)	0·001
Lowest heart rate during first surfactant treatment (beats per min)¶	139 (120–157)	146 (140–160)	0·010
Lowest SpO_2 during first surfactant treatment (%)‖	80 (70–87)	84 (77–88)	0·057

Data are number (%) or median (IQR). FiO_2=fraction of inspired oxygen. SpO_2=saturation of peripheral oxygen. *Intraventricular haemorrhage grade 3 or 4; periventricular leukomalacia, necrotising enterocolitis or focal intestinal perforation treated with surgery; retinopathy of prematurity treated with laser or cryocoagulation; or death. †Pneumothorax, pneumopericardium, pulmonary haemorrhage, congenital abnormalities, other life-threatening events, and events that might result in permament disability. ‡Data restricted to infants who were treated with surfactant. §FiO_2 at first surfactant treatment was recorded in 69 of 73 infants in the standard treatment group and 78 of 80 infants in the intervention group. ¶Heart rate during surfactant application was recorded in 63 of 73 infants of the standard treatment group and 76 of 80 infants in the intervention group. ‖SpO_2 during surfactant application was recorded in 61 of 73 infants of the standard treatment group and 77 of 80 infants in the intervention group.

Table 4: **Secondary outcomes—drug treatments and serious adverse events**

intubate–surfactant–extubate technique seems to be more invasive than our method and was not better than CPAP and rescue intubation in the CURPAP trial (table 5).[9] By contrast with the method used in our trial, which is done during spontaneous breathing, mechanical ventilation or bagging are done after surfactant administration by the intubation, surfactant, and extubation approach, which might be harmful to an immature lung. Pharyngeal deposition of surfactant[23] and the application of surfactant via a laryngeal mask[24,25] have only been tested in small, observational pilot studies. The application of aerosolised surfactant is still a technical challenge and nebulisation of surfactant has not been successful so far, probably because of low deposition rates.[26]

Panel: Research in context

Systematic review

We searched Medline from 1996, to 2011, for full studies reporting randomised clinical trials with the terms "surfactant", "ventilation", and "preterm infant". None of the 86 trials assessed surfactant application to spontaneously breathing preterm infants. A meta-analysis[21] of the intubate–surfactant–extubate method, which differs from the technique used in our trial, was published in 2009. Our report is the first randomised trial testing the effect of surfactant application to spontaneously breathing infants on the subsequent need for mechanical ventilation.

Interpretation

Observational data[5–7,12] suggest that surfactant application to spontaneously breathing preterm infants might improve pulmonary outcome. Our trial shows that application of surfactant to spontaneously breathing preterm infants is feasible, and reduces the need for mechanical ventilation, the duration of mechanical ventilation, and oxygen requirement at 28 days of age. Furthermore, this technique resulted in a higher rate of surfactant treatment and a lower rate of mechanical ventilation compared with other trials (table 5).

Reduced mechanical ventilation and bronchopulmonary dysplasia have been reported by neonatal intensive care units that routinely use nasal CPAP.[12,27] The COIN trial[2] and the SUPPORT trial[3] included large cohorts of preterm infants who were randomly assigned to either nasal CPAP or intubation. In both trials, the surfactant treatment rate was lower in the CPAP group than in the intubation group (table 5). Rates of the primary outcome—death or bronchopulmonary dysplasia—did not differ between the CPAP and intubation groups.[2,3]

Preterm infants in our trial had a short duration of mechanical ventilation and a low rate of bronchopulmonary dysplasia or death compared with COIN, SUPPORT, and other trials that use bronchopulmonary dysplasia as their primary outcome (table 5).[28] However, similar to the meta-analysis of the intubate–surfactant–extubate technique, treatment of infants with an FiO_2 greater than 0·30 might lead to overuse of surfactant. Our protocol favoured treatment of respiratory distress syndrome at an early stage, rather than late (rescue) treatment.

Bronchopulmonary dysplasia was not the primary outcome in the our trial because the low incidence in infants older than age 26 weeks would have needed a substantially larger sample size. However, retrospective observational data[15] and the low rate of supplementary oxygen given at 28 days in our trial suggest that infants of a low gestational age who receive surfactant while spontaneously breathing might also benefit in terms of long-term pulmonary outcome. In view of the efficacy and safety of the procedure in our trial, a subsequent

	AMV (26–28 weeks)		SUPPORT[3] (26–27 week stratum)		COIN[2] (27–28 week stratum)		CURPAP[9] (25–28 weeks)	
	CPAP, surfactant without intubation (n=108)	CPAP with rescue intubation (n=112)	CPAP with rescue intubation (n=378)	Intubation (n=373)	CPAP with rescue intubation (n=207)	Intubation (n=198)	CPAP with rescue intubation (n=103)	Intubation, early extubation (n=105)
Birthweight (g; mean [SD])	975 (244)	938 (205)	834 (188)*	825 (198)*	964 (212)*	952 (217)*	913 (200)	967 (221)
Surfactant treatment (%)	74%	65%	67%*	99%*	38%*	77%*	49%	100%
Mechanical ventilation (%)	33%	73%	83%*	100%*	59%*	100%*	33%	100%
Days on mechanical ventilation (median [IQR])	0 (0–3)	2 (0–5)	4 (0–15)	6 (2–21)	3 (0–11)*	4 (1–14)*	6 (1–112)†	5 (1–61)†
Pneumothorax (%)	4%	7%	6%	6%	9%*	3%*	1%	7%
Bronchopulmonary dysplasia at 36 weeks or death (%)	14%	15%	38%	44%	25%	31%	21%	22%

CPAP=continuous positive airway pressure. CPAP with rescue intubation was the intervention in the SUPPORT and COIN trials, but was the control in the AMV and CURPAP trials. *Data are for all infants in the trial (gestational age 24–27 weeks in SUPPORT, 25–28 weeks in COIN). †In the CURPAP trial, days on mechanical ventilation are medians (range) for intubated infants.

Table 5: **CPAP, surfactant treatment, and outcome data from published trials**

study in infants between 23 and 26 weeks of gestation (ISRCTN:64011614) has been started. In this subgroup, bronchopulmonary dysplasia incidence is high,[2] enabling the investigators to test whether less ventilation after surfactant replacement during spontaneous breathing can reduce rates of bronchopulmonary dysplasia.

Heart rates and SpO_2 were recorded during surfactant delivery but not during intubation. Success of endotracheal intubation at the first attempt during neonatal resuscitation can be as low as 62%, and the heart rate or SpO_2 of about 50% of all infants undergoing endotracheal intubation deteriorates during the procedure.[29] Compared with these data, the failure rate of surfactant application without ventilation was low in our study. However, mean heart rate and mean SpO_2 during surfactant application were slightly lower in the intervention group than in the standard treatment group, which is not surprising because control of respiration and oxygenation is easier to achieve in an intubated infant than in a spontaneously breathing infant. Although the side-effects of the intervention were moderate, the method should be done only by neonatologists who are proficient in airway management of preterm infants, including endotracheal intubation.

Our trial has several limitations. We could not mask the study intervention. Therefore, subsequent care might have been biased by knowledge of randomisation. However, the intubation rate, median time receiving mechanical ventilation, and duration of oxygen supplementation in the standard treatment group was low compared with published data (table 5).[2,3] As in many multicentre studies, treatment standardisation was difficult. However, infants were randomly assigned and exposed to identical treatment in both groups. Logistic regression analysis showed no significant centre effects. The effectiveness of the procedure was similar in centres using a threshold of FiO_2 of 0·40 or less, or FiO_2 more than 0·40 for rescue intubation and surfactant application. Only one infant was outborn and transported, and almost all mothers received antenatal glucocorticoids. Therefore, our findings should not be generalised to infants who are not born in a level 3 neonatal intensive care unit and do not receive antenatal steroids.

Although we cannot exclude that early extubation of some infants in the standard treatment group might have been difficult to achieve because of the increased treatment with analgesics and sedatives, secondary analyses (webappendix p 3) suggest that sedation or analgesia do not affect the primary outcome. However, the low rate sedation or analgesia in the intervention group might be of benefit, because a drop in blood pressure and impaired cerebral perfusion are potential hazards of analgesia and sedation in very immature infants.[30] A study describes a decrease in brain electrical activity in infants undergoing an intubation, surfactant, extubation procedure, which the investigators attribute to the medication used for intubation rather than the method itself.[31]

In the future, surfactant given to spontaneously breathing preterm infants via a thin diameter tube might be included in individualised and gentler care for preterm infants.

Contributors

WG and EH were the principal investigators of the study. WG, EH, AK, and BR conceived and designed the study; and did the data gathering, analysis, and interpretation, and prepared and approved the report. AZ was the primary statistician, CH and SH participated in data gathering and analysis, and prepared and approved the report. All other authors contributed to study design, data gathering, analyses, and interpretation, and prepared and approved the report.

Additional members of the AMV Study group

Trial investigators: *University of Lübeck* IR König, G Stichtenoth, M Bendiks; *Kinderkrankenhaus auf der Bult, Hannover* E Kattner; *Olgahospital, Stuttgart* T Strahleck; *University of Cologne, Cologne* K Mehler, C Hünseler; *University of Düsseldorf, Düsseldorf* B Hadzik; *Klinik für Kinder- und Jugendmedizin, Aschaffenburg* Katja Moser; *University of Magdeburg, Magdeburg* K Buder, S Lenze; *Altonaer Kinderkrankenhaus, Hamburg* E Raedler, P Gudowius; *Klinik für Kinder- und Jugendmedizin, Saarbrücken* D Anhalt. Designated trial sites without patient enrolment: *University of Bochum* N Teig; *Christian Albrechts University, Kiel* W Nikischin. Data and safety monitoring committee: *University of Dresden* M Rüdiger; *University of Lübeck* A Katalinic.

Conflicts of interest

EH has received speaking fees and travel grants from the surfactant-producing companies Abbot, Chiesi, Nycomed, Boehringer, and Altana. EH has participated in clinical trials sponsored by Abbott, Boehringer, Chiesi, Byk Gulden, Altana, and Nycomed. EH has worked on advisory boards for Chiesi, Nycomed, and Draeger Medical, a company working in the field of neonatal ventilation, monitoring, and thermal care. EH received no money personally for this study, the support was institutional to cover insurance and other regulatory costs of the trial.

Acknowledgments

The trial was supported by grants from Chiesi Pharmaceuticals, Lübeck University, and the German Ministry of Research and Technology (grant number 01ER0805, The German Neonatal Network). Chiesi Pharmaceuticals is a manufacturer of surfactant. We thank all the staff in participating hospitals and especially the parents and infants who participated in the trial.

References

1 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet* 2009; **374:** 250–59.

2 Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008; **358:** 700–08.

3 Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010; **362:** 1970–79.

4 Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database Syst Rev* 2009; **2:** CD007836.

5 Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics* 2009; **123:** 137–42.

6 Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics* 2004; **113:** e560–63.

7 Reininger A, Khalak R, Kendig JW, et al. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. *J Perinatol* 2005; **25:** 703–08.

8 Escobedo MB, Gunkel JH, Kennedy KA, et al. Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter, randomized trial. *J Pediatr* 2004; **144:** 804–08.

9 Sandri F, Plavka R, Ancora G, et al, for the CURPAP study group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics* 2010; **125:** e1402–09.

10 Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. *N Engl J Med* 1994; **331:** 1051–55.

11 Stevens TP, Harrington EW, Blennow M, Soll R. 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* 2007; **4:** CD003063.

12 Ammari A, Suri M, Milisavljevic V, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005; **147:** 341–47.

13 Kribs A, Pillekamp F, Hünseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age </=27 weeks). *Paediatr Anaesth* 2007; **17:** 364–69.

14 Kribs A, Vierzig A, Hünseler C, et al. Early surfactant in spontaneously breathing with nCPAP in ELBW infants—a single centre four year experience. *Acta Paediatr* 2008; **97:** 293–98.

15 Kribs A, Härtel C, Kattner E, et al. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. *Klin Paediatr* 2010; **222:** 13–17.

16 Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004; **114:** 1305–11.

17 Jung SH, Ahn C, Donner A. Evaluation of an adjusted chi-square statistic as applied to observational studies involving clustered binary data. *Stat Med* 2001; **20:** 2149–61.

18 Dahmen G, Ziegler A. Generalized estimating equations in controlled clinical trials: hypotheses testing. *Biomed J* 2004; **46:** 214–32.

19 Verder H, Agertoft L, Albertsen P, et al. Surfactant treatment of newborn infants with respiratory distress syndrome primarily treated with nasal continuous positive air pressure. A pilot study. *Ugeskr Laeger* 1992; **154:** 2136–69.

20 Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. *Arch Dis Child Fetal Neonatal Ed* 2011; **96:** F243–48.

21 Soll RF. Current trials in the treatment of respiratory failure in preterm infants. *Neonatology* 2009; **95:** 368–72.

22 Halliday HL. Surfactants: past, present and future. *J Perinatol* 2008; **28** (suppl 1): S47–56.

23 Kattwinkel J, Robinson M, Bloom BT, Delmore P, Ferguson JE. Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. *J Perinatol* 2004; **24:** 360–65.

24 Brimacombe J, Gandini D, Keller C. The laryngeal mask airway for administration of surfactant in two neonates with respiratory distress syndrome. *Paediatr Anaesth* 2004; **14:** 188–90.

25 Trevisanuto D, Grazzina N, Ferrarese P, Micaglio M, Verghese C, Zanardo V. Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. *Biol Neonate* 2005; **87:** 217–20.

26 Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta Paediatr* 2000; **89:** 460–64.

27 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics* 1999; **103:** 961–67.

28 Mercier JC, Hummler H, Durrmeyer X, et al, for the EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet* 2010; **376:** 346–54.

29 O'Donnell CPF, Kamlin COF, Davis PG, Morley CJ. Endotracheal intubation attempts during neonatal resuscitation: success rates, duration, and adverse effects. *Pediatrics* 2006; **117:** e16–21.

30 Welzing L, Kribs A, Elfinger F, Huenseler C, Oberthuer A, Roth B. Propofol as an induction agent for endotracheal intubation can cause significant artierial hypotension in preterm neonates. *Paediatr Anaesth* 2010; **20:** 605–11.

31 Van den Berg E, Lemmers PM, Toet MC, Klaessens JH, van Bel F. Effect of the InSurE procedure on cerebral oxygenation and electrical brain activity of the preterm infant. *Arch Dis Child Fetal Neonatal Ed* 2010; **95:** F53–58.