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ORIGINAL ARTICLE

Implementation of surfactant treatment during continuous positive airway pressure

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Objective: To study the effects of implementing a method for surfactant administration by transient intubation, INSURE (i.e. INtubation SURfactant Extubation) during nasal continuous positive airway pressure (nCPAP) for moderately preterm infants with respiratory distress syndrome (RDS).

Study design: A descriptive, retrospective, bi-center study in Stockholm, Sweden, comparing mechanical ventilation (MV) rates, surfactant use, treatment response and outcome of all inborn infants with gestational age 27 to 34 weeks and RDS, ($n = 420$), during the 5-year periods before and after the introduction of the INSURE-strategy at one of the centers (Karolinska Huddinge) in 1998. The other center (Karolinska Solna) continued conventional surfactant therapy in conjunction with MV throughout the study.

Results: Implementation of INSURE at Karolinska Huddinge reduced the number of infants requiring MV by 50% ($P<0.01$), resulted in earlier surfactant administration and increased overall surfactant use. INSURE-treatment improved oxygenation and the treatment response was sustained over time with only 17% of the infants requiring >1 dose of surfactant. At Karolinska Solna, the MV rates were unaltered between the first and second 5-year period.

Conclusion: Implementing a strategy of surfactant administration by transient intubation during nCPAP reduces the need for MV without adverse effects on outcome and may be an option to more effectively treat RDS, particularly in a care setting where transfer is necessary to provide MV.

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Introduction

Surfactant is administered to neonates by tracheal instillation as trials with nebulized surfactant have not yet been successful.[1,2] Tracheal instillation requires an endotracheal tube to be placed; hence surfactant is usually administered at initiation of or during mechanical ventilation (MV). However, MV in itself may induce varying degrees of lung injury, with epithelial disruption followed by fluid leakage and inflammatory response that can inactivate surfactant.[3,4] We have previously shown that in premature rabbits, surfactant administration followed by MV resulted in impaired treatment response and a greater degree of surfactant inactivation than surfactant treatment followed by spontaneous breathing.[5] Furthermore, MV has been implicated as the single most important risk factor for the later development of bronchopulmonary dysplasia (BPD).[6,7]

Surfactant treatment of spontaneously breathing infants by transient intubation was first reported in 1990 in a study performed in Kuwait, where MV was not available at the time.[8] In 1994, Verder *et al*.[9] published the first randomized controlled trial of surfactant instillation during nasal continuous positive airway pressure (nCPAP) showing that in infants with moderate-to-severe respiratory distress syndrome (RDS), the need for subsequent MV could be reduced by half after a single dose of surfactant. The effect was even more pronounced if the surfactant treatment was given early in the course of the disease.[10] More recent randomized trials have confirmed these results and in addition showed a reduction in the need for repeated surfactant doses.[11,12]

In Scandinavia, early nCPAP is the first line of treatment for very low-birth-weight infants and many infants can be successfully managed without MV.[13,14] In 1997, Jonsson *et al*.[14] evaluated ventilatory treatment strategies for all infants with a birth weight <1500 g in Stockholm County. Of infants receiving early nCPAP treatment, 34% later required MV and failure of nCPAP was significantly associated with the presence of RDS. Of infants with the diagnosis of RDS cared for at neonatal units in Stockholm without available MV, 85% had a gestational age of ⩾27 weeks and 91% required transfer for neonatal intensive care.[14] The majority of these infants would likely have benefited from surfactant therapy.

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Thus, the present study targeted the moderately preterm infants with RDS, gestational age 27 to 34 weeks. In Stockholm, RDS is managed with early nCPAP and, if necessary, rescue surfactant treatment in conjunction with MV. In 1998, a modified protocol adopted from Verder *et al*., was implemented in a neonatal unit without available MV. The new treatment strategy, with surfactant administration by transient intubation during nCPAP, was labeled INSURE (that is INtubation SURfactant Extubation). We hypothesized that INSURE-treatment would reduce the need for MV and allow for earlier surfactant treatment. The study was designed as a retrospective follow-up of all inborn infants diagnosed with RDS during a 10-year period, 1993 to 2002, comparing the 5-year period before and after the introduction of INSURE.

Materials and methods

Study populations

Stockholm County has five delivery units and approximately 25 000 deliveries per year. At Karolinska University Hospital in Stockholm:

Karolinska Solna (KS) provides neonatal care for the central and northwestern parts of Stockholm County. KS is the regional referral center for infants born <27 weeks of gestation and was, at the time of the study, the only unit in Stockholm providing MV.

Karolinska Huddinge (KH) provides neonatal care for the south and southwestern parts of Stockholm County. KH is a unit staffed with accredited neonatologists and neonatal nurses skilled in nCPAP and cares primarily for infants $\geqslant$27 weeks gestation.

As MV was not available at KH at the time of the study, all infants requiring MV needed to be transferred to KS. In 1998, the INSURE strategy for surfactant administration was implemented at KH. To evaluate the effects of this new treatment strategy, a 5-year period before and after the start of INSURE was studied. Charts were reviewed from all inborn infants with gestational age 27 weeks + 0 days to 33 weeks + 6 days between 1993 and 2002 at KH. Infants with RDS, defined as tachypnea and/or grunting, increasing demand of oxygen and characteristic radiographic findings,[15] were included ($n = 155$). Exclusion criteria were major congenital malformations or chromosomal abnormalities. MV rates, duration of ventilatory support, incidence of BPD and other complications were compared for the time periods before (1993 to 1997) and after (1998 to 2002), the introduction of INSURE. Treatment response was evaluated by an oxygenation index (the arterial to alveolar ratio) for the 48 h following the surfactant therapy.

KH and KS collaborated closely regarding general care routines, however, the INSURE strategy was not implemented into general practice at KS before the year of 2002. For comparison and to assess the impact of changing care practices over time, inborn infants at KS during the 1993 to 2002 meeting the inclusion criteria (gestational age 27 to 33 weeks and RDS as described above) were reviewed ($n = 265$) and the same 5-year periods as for KH (1993 to 1997 and 1998 to 2002) were compared.

The Human Ethical Committee at the Karolinska Institute approved the study.

Criteria for nCPAP, MV and surfactant treatment

Early nCPAP use was practiced, that is, preterm infants with respiratory distress were started on nCPAP soon after birth, usually in the delivery ward. Initial pressures were set to 3 to 5 cm H_2O using the Infant Flow system (EME, Brighton, UK) or a Benveniste jet system.[16] The fraction of inspired oxygen (F_{iO_2}) was adjusted to give an arterial or transcutaneous partial pressure of oxygen (P_{O_2}) value of 8 to 10 kPa (60 to 75 mm Hg). The oxygenation was assessed by the arterial to alveolar ratio (a/A ratio), calculated as:

$$\text{a/A ratio} = P_{aO_2}/(F_{iO_2} \times 95) - P_{aCO_2}$$

(P_{aO_2} is the arterial partial pressure of oxygen, F_{iO_2} the fraction of inspired oxygen and P_{aCO_2} the arterial partial pressure of carbon dioxide).

From 1998, infants at KH were eligible for INSURE surfactant treatment (Curosurf, Chiesi Farmaceutici, Parma, Italy) when the a/A ratio was 0.22 or less. This corresponds to an F_{iO_2} of approximately 0.45 with normal partial pressures of O_2 and CO_2. Infants requiring intubation as part of resuscitation at birth were not considered for INSURE. The criteria for MV were P_{aCO_2} exceeding 8.5 kPa (approximately 65 mm Hg) and $F_{iO_2 > 0.6}$, or signs of severe respiratory distress or apneas. At that point, infants at KH were transferred to KS for MV.

The INSURE procedure

Intravenous access was required for drug administration and an arterial line for therapeutic control. A loading dose of theophylline, 5 to 7 mg/kg intravenously (i.v.) was given at start of the procedure to prevent apnea. Infants were anaesthetized with morphine 0.2 mg/kg i.v. and sedated with pentobarbital (that is thiopental), 2 mg/kg i.v, repeated as needed up to 5 mg/kg. Intubation was performed orally. The tube position was evaluated by auscultation of the chest. Surfactant, 100 to 200 mg/kg of Curosurf (a full vial was given within the dosage limits), was administered as a bolus tracheal instillation. The infants were briefly ventilated manually with controlled inspiratory pressure (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare Ltd, Auckland, New Zealand), while naloxone 0.1 mg/kg i.v. was given to reverse the opiate induced respiratory depression. Extubation to continued nCPAP was then performed immediately. The whole procedure from intubation to extubation was usually completed within 4 to 6 min. Intubation as part of resuscitation at birth was not regarded as INSURE.

Outcome parameters

INSURE failure was defined as need for MV (according to criteria above) during the first week after surfactant treatment. The duration of MV and CPAP was recorded. BPD was defined as oxygen requirement at 36 weeks post-menstrual age.[17] Repeated cranial ultrasounds were performed during the first 2 weeks of life and

intraventricular hemorrhage (IVH) was defined and graded according to Papile *et al*.[18] IVH grade III or more was reported. Infants were screened for retinopathy of prematurity (ROP) at 4 weeks of age and thereafter once weekly as needed until vascularization was complete.[19] ROP requiring treatment with laser or cryotherapy (stage III or more) was reported. Mortality was defined as death before discharge.

Statistical analyses

Results are shown as mean±standard deviation (s.d.), if not otherwise specified. Two-tailed Student's *t*-tests were used for normally distributed data, Mann–Whitney *U*-tests for non-normally distributed data, χ^2- and Fisher's exact test for categorical data. Statistical analyses were performed using SPSS (version 11.5, SPSS Inc., Chicago, IL, USA) and Stat graphics (Manugistics Inc., Rockville, ML, USA).

Results

After the introduction of INSURE in 1998, the need for MV at KH was reduced by half, from 38 to 19%, $P<0.01$ (Table 1). During the second time period, 1998 to 2002, surfactant therapy was given at an earlier age and thereby likely at less severe stage of the RDS, as reflected by a higher oxygenation ratio (a/A ratio) before treatment. On the other hand, in the latter time period, the patients were also slightly more immature with a 1-week difference in gestational age and an average birth weight of 250 g less compared with the patients in the first time period (Table 1). Outcome in terms of number of days with ventilatory support, complications and death were unaltered after the introduction of INSURE (Table 1).

At the referral center, KS, where the INSURE approach was not practiced, the MV rate in the population of infants with RDS and gestational age 27 to 34 weeks remained unchanged between the first and second time periods (Table 2). The trend for the infants to be more immature during the latter time period was evident at the referral center as well, however, age and disease severity at initiation of surfactant treatment did not change over the time periods (Table 2). Differences in pregnancy risks and complications between time period and centers could not be controlled for with the retrospective study design. Of all included infants, the number that was delivered by cesarean section varied between 74 and 85%, the number of infants being products of multiple pregnancies varied between 20 and 31% and average Apgar scores at 5 min were 8 to 9. There were no significant differences between time periods or centers (data not shown).

Forty-two infants at KH received surfactant according to the INSURE protocol and eight infants received surfactant either as part of resuscitation at birth or after already being placed on MV. Eight infants (19%) were considered failures, that is, went on to require MV. Among those, two had reasons for failure other than

Table 1 Before and after the introduction of INSURE at KH

	1993–1997 (n = *74*)	*1998–2002* (n = *81*)	P
Population characteristics			
Gestational age (weeks)	30.4±2.0	29.2±1.8	<0.01
Birth weight (g)	1590±452	1333±392	<0.01
Antenatal steroids (%)	66	73	0.44
Treatment characteristics			
Mechanical ventilation, *n* (%)	28 (38)	15 (19)	<0.01
Surfactant, *n* (%)	18 (24)	50 (62)	<0.01
Age at first dose surfactant (h)	25±20	12±10	0.01
a/A ratio before surfactant	0.10±0.05	0.17±0.06	<0.01
Outcome			
BPD, *n* (%)	6 (8)	10 (12)	0.44
Air leaks, *n* (%)	11 (15)	11 (14)	0.82
IVH, *n* (%)	4 (5)	3 (4)	0.87
ROP, *n* (%)	0 (0)	2 (2)	0.17
Mortality, *n* (%)	1 (1)	2 (2)	0.61

Abbreviations: INSURE, INtubation SURfactant Extubation; KH, Karolinska Huddinge; a/A, arterial to alveolar; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.
Mean±s.d., if not otherwise specified.

Table 2 Changes over time at the referral center, KS, without INSURE

	1993–1997 (n = *156*)	*1998–2002* (n = *109*)	P
Population characteristics			
Gestational age (weeks)	29.7±2.1	29.2±1.9	0.05
Birth weight (g)	1499±539	1325±423	0.01[a]
Antenatal steroids (%)	32	69	>0.01
Treatment characteristics			
Mechanical ventilation, *n* (%)	92 (59)	72 (66)	0.24
Surfactant, *n* (%)	78 (50)	73 (67)	<0.01
Age at first dose surfactant (h)	17±15	15±13	0.45
a/A ratio before surfactant	0.13±0.08	0.15±0.13	0.30
Outcome			
BPD, *n* (%)	22 (14)	18 (17)	0.59
Air leaks, *n* (%)	34 (22)	20 (18)	0.49
IVH, *n* (%)	4 (3)	4 (4)	0.60
ROP, *n* (%)	6 (4)	4 (4)	0.94
Mortality, *n* (%)	12 (8)	6 (6)	0.49

Abbreviations: KS, Karolinska Solna; INSURE, INtubation SURfactant Extubation; a/A, arterial to alveolar; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.
Mean±s.d., if not otherwise specified.
[a]Mann–Whitney *U*-test.

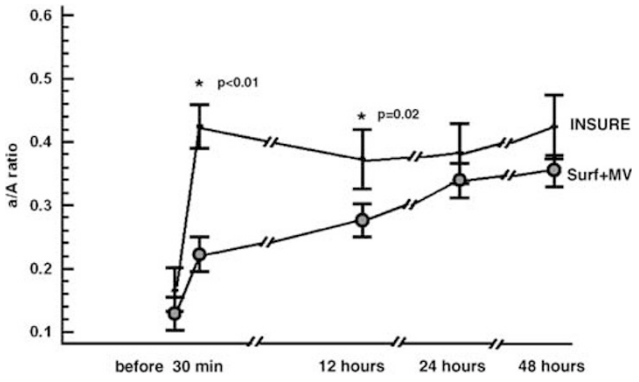

Figure 1 Infants receiving INSURE treatment (—) and infants receiving conventional surfactant treatment followed by MV (○). The oxygenation, as determined by the arterial to alveolar ratio (a/A ratio), was similar at the time of surfactant administration and improved following treatment. In INSURE-treated infants, the immediate improvement in oxygenation 30 min after treatment was more pronounced compared with S + MV infants, shown by a significantly higher a/A ratio ($P<0.01$). The improved oxygenation was sustained after INSURE over the 48 h following the surfactant treatment.

deteriorating respiratory distress. One infant had his nose severely squeezed during delivery, which impaired the function of the nasal CPAP and a second child accidentally received too high a dose of pentobarbital resulting in impaired respiratory drive, which prevented extubation. No infant received surfactant by the INSURE procedure more than once. It was decided that if an infant's respiratory status deteriorated to meet the criteria for a second dose of surfactant, the infant was to be kept intubated after surfactant administration, transferred for MV and considered as an INSURE failure.

After the introduction of INSURE, significantly more infants received surfactant at KH, 62 versus 24% (Table 1). However, only 17% of the INSURE-treated infants required more than one dose of surfactant. This is to be compared with infants at KS during 1998 to 2002 who all received surfactant in conjunction with MV of which 58% required multiple doses (data not shown). The overall use of surfactant increased at KS as well, from approximately 1/2 in the first time period to 2/3 of the patients in the second time period receiving surfactant treatment.

INSURE-treated infants exhibited a rapid and sustained improvement in oxygenation following the surfactant administration. Contemporary infants at the referral center KS receiving conventional surfactant treatment during MV showed a slower and less pronounced improvement in oxygenation (Figure 1).

Discussion

By implementing a treatment strategy of surfactant administration by transient intubation during nCPAP (INSURE), the need for MV in moderately preterm infants is effectively reduced. Furthermore, the INSURE approach resulted in a decreased requirement of surfactant re-treatment, which may be the effect of a more pronounced and sustained improvement in oxygenation compared with conventional surfactant treatment followed by MV.

Our results confirm the previously reported data.[9–12] In the first randomized study of the INSURE approach by Verder *et al*.,[9] surfactant was administered at an a/A ratio of 0.22. In our protocol, infants were eligible for surfactant treatment at the same level of oxygenation, however in retrospect, the a/A ratio just before surfactant treatment was lower (overall approximately 0.15). As earlier rescue treatment at an a/A ratio of 0.36 was shown to be even more effective in reducing the need for MV,[10] it is possible that our results could have been improved further had the surfactant been administered at a higher a/A ratio. Along the same line, the earlier surfactant treatment accomplished by INSURE may, in itself, be an important factor for the reduction in MV rate seen in the second time period. Early versus delayed surfactant treatment also appears to reduce the risk of complications and improve outcome.[20] However, the approach with prophylactic or very early rescue administration of surfactant carries a risk of treating infants whose disease progress would not warrant surfactant, which has both ethical and economical consequences. This is likely to be particularly important for infants with gestational age $\geqslant 27$ weeks and, in fact, early nCPAP alone will prevent progression to respiratory failure in many infants and in combination with antenatal steroids, the number of infants without clinical symptoms of RDS is further decreased.[21] Previous data from our region shows that approximately 1/3 of infants with RDS do well with nCPAP as only ventilatory support.[14] We choose to administer surfactant as rescue treatment to infants with moderate to severe RDS. This is similar to the late-treated group reported by Verder *et al*.[10] who received surfactant at a median age of 9.9 h (compared with 12 h after the introduction of INSURE 1998 to 2002) and had an a/A ratio at the time of treatment of 0.16 (0.17 in the present study). Only 19% of the KH infants progressed to needing MV after introduction of INSURE compared with 68% of the late-treated infants in the Danish study.[10] The Danish population was slightly more immature, which might have contributed to the difference. Of the early-treated in the Danish study, 25% needed MV, which is in the same range as at KH after the INSURE-procedure was implemented. A rapid test of lung maturity that accurately predicts the risk of developing clinically significant RDS would, in the future, allow for early or prophylactic surfactant treatment of infants at risk.[22] As a mode of surfactant administration, the INSURE approach would then provide a means to avoid potentially harmful MV and possibly reduce the need for transfers of moderately preterm infants to an intensive care facility.

This study has several limitations. It is retrospective in design and therefore uses a nonrandomized, historical control group. We believe that its value lies in the long-term evaluation of the

implementation of a new treatment strategy previously shown to be beneficial in randomized control trials.[9–12] The two centers providing different levels of intensive care may have been a confounding variable affecting care practices other than surfactant management. However, there was a close working relationship between the two centers, and routines regarding the moderately preterm infants were similar. The antenatal services at the two centers cared for high-risk pregnancies and although differences in pregnancy complications could not be controlled for, the rates of caesarean sections, multiple pregnancies and antenatal steroid use did not differ.

Surfactant treatment improved oxygenation in all subjects although the treatment response appeared to be augmented after INSURE (Figure 1). It has to be taken into consideration that the conventionally treated infants come from another center than the INSURE infants and that the patient-population therefore may have had pre- and postnatal risk factors that could not be controlled for with the present study design. However, we believe it to be an interesting observation that warrants further study. In experimental settings, ventilation strategy can clearly alter the treatment response of exogenous surfactant. In lambs, MV with large tidal volumes before surfactant administration comprises the therapeutic effect.[23] Animal studies of CPAP are very sparse, but in a recent report Jobe *et al*.[24] found more neutrophils and higher levels of hydrogen peroxide in alveolar washes from mechanically ventilated preterm lambs compared with CPAP-treated, indicating more severe lung injury in the former group, with possible disruption of the surfactant system as a consequence. We have previously reported the impaired tissue association of exogenous surfactant in preterm rabbits after MV compared with spontaneous breathing.[5] This finding was associated with a lower dynamic compliance and evidence of surfactant inactivation and constitutes a possible explanation to an attenuated treatment response after surfactant administration followed by MV. These data demonstrate that the immediate improvement in oxygenation following INSURE was sustained over the 48 h following treatment, which may have contributed to the low requirement for surfactant re-treatment. Our results are supported by previous studies of surfactant together with nCPAP in which a single dose was sufficient to reverse the clinical course of RDS in most patients,[9,10] whereas in mechanically ventilated infants, multiple doses are often required.[25] It is also in line with the results of Dani *et al*.[11] from a recent randomized trial showing that none of the infants with immediate reinstitution of nCPAP after surfactant administration required a second treatment dose compared with 50% in infants receiving MV after surfactant treatment. However, the overall use of surfactant increased significantly after the introduction of INSURE, which is consistent in the most recent meta-analysis comparing early surfactant administration with brief MV to later, selective surfactant treatment followed by continued MV.[26] The increase in surfactant use may have contributed to the reduction in MV rates, but availability of surfactant treatment to more patients and treatment earlier in the course of the disease are also desirable effects linked to the concept of INSURE. The overall increase in surfactant use may also not be entirely attributable to the introduction of INSURE as an increased surfactant use in the latter time period was noted at KS as well.

The implementation of INSURE could not be shown to reduce the incidence of BPD in our cohort of infants and neither has a similar approach in any previous randomized trials.[9,10,12,26] The development of BPD is complex and multifactorial, thus the impact of INSURE compared with modern MV strategy may not be evident. Neither in other outcome parameters, such as IVH, ROP and mortality, could any changes be detected. Outcome parameters at the referral center KS also remained similar over time suggesting no major impact of other changes in care practices.

In conclusion, a treatment strategy of surfactant administration by transient intubation during nCPAP (INSURE) is a safe alternative to surfactant treatment followed by MV in moderately preterm infants. INSURE significantly reduces the need for MV with no adverse effects on the outcome. For smaller neonatal units, the INSURE approach is an option to administer surfactant earlier and effectively treat RDS, particularly in a care setting where transfer is needed for MV. This holds the benefit of a possible reduction in costs and, more importantly, will facilitate a family-centered neonatal care. INSURE may provide a means to optimize regional neonatal intensive care without increasing the need for transportation of moderately preterm infants with RDS. Experience, a good CPAP program and ventilator back up is still a prerequisite in the care of these patients.

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