Lung recruitment before surfactant administration in extremely preterm neonates with respiratory distress syndrome (IN-REC-SUR-E): a randomised, unblinded, controlled trial

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Summary

Background The importance of lung recruitment before surfactant administration has been shown in animal studies. Well designed trials in preterm infants are absent. We aimed to examine whether the application of a recruitment manoeuvre just before surfactant administration, followed by rapid extubation (intubate-recruit-surfactant-extubate [IN-REC-SUR-E]), decreased the need for mechanical ventilation during the first 72 h of life compared with no recruitment manoeuvre (ie, intubate-surfactant-extubate [IN-SUR-E]).

Methods We did a randomised, unblinded, controlled trial in 35 tertiary neonatal intensive care units in Italy. Spontaneously breathing extremely preterm neonates (24+0 to 27+6 weeks' gestation) reaching failure criteria for continuous positive airway pressure within the first 24 h of life were randomly assigned (1:1) with a minimisation algorithm to IN-REC-SUR-E or IN-SUR-E using an interactive web-based electronic system, stratified by clinical site and gestational age. The primary outcome was the need for mechanical ventilation in the first 72 h of life. Analyses were done in intention-to-treat and per-protocol populations, with a log-binomial regression model correcting for stratification factors to estimate adjusted relative risk (RR). This study is registered with ClinicalTrials.gov, NCT02482766.

Findings Of 556 infants assessed for eligibility, 218 infants were recruited from Nov 12, 2015, to Sept 23, 2018, and included in the intention-to-treat analysis. The requirement for mechanical ventilation during the first 72 h of life was reduced in the IN-REC-SUR-E group (43 [40%] of 107) compared with the IN-SUR-E group (60 [54%] of 111; adjusted RR 0·75, 95% CI 0·57–0·98; p=0·037), with a number needed to treat of 7·2 (95% CI 3·7–135·0). The addition of the recruitment manoeuvre did not adversely affect the safety outcomes of in-hospital mortality (19 [19%] of 101 in the IN-REC-SUR-E group *vs* 37 [33%] of 111 in the IN-SUR-E group), pneumothorax (four [4%] of 101 *vs* seven [6%] of 111), or grade 3 or worse intraventricular haemorrhage (12 [12%] of 101 *vs* 17 [15%] of 111).

Interpretation A lung recruitment manoeuvre just before surfactant administration improved the efficacy of surfactant treatment in extremely preterm neonates compared with the standard IN-SUR-E technique, without increasing the risk of adverse neonatal outcomes. The reduced need for mechanical ventilation during the first 72 h of life might facilitate implementation of a non-invasive respiratory support strategy.

Funding None.

Introduction

The American Academy of Pediatrics Committee on the Fetus and Newborn emphasises the use of continuous positive airway pressure (CPAP) immediately after birth with subsequent selective surfactant administration as an alternative to routine intubation with prophylactic or early surfactant administration in preterm neonates.[1] When given, surfactant should be distributed homogeneously in the lung and invasive mechanical ventilation at the time of surfactant administration should be as short as possible.

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Research in context

Evidence before this study

The most effective strategy for established respiratory distress syndrome (RDS) is early rescue surfactant therapy administered to infants receiving nasal continuous positive airway pressure (CPAP) immediately after birth using a sequence such as intubation-surfactant-extubation (IN-SUR-E). However, IN-SUR-E might not be successful because of lung de-recruitment during intubation, which impedes surfactant distribution and efficacy. Preclinical studies show lung recruitment before surfactant administration improved gas exchange and lung function as a consequence of more homogeneous surfactant distribution. We searched MEDLINE (via PubMed), Embase, and the Cochrane Central databases for clinical trials published in English between Jan 1, 2010, and June 1, 2015, using the terms "surfactant", "preterm infants", and "respiratory distress syndrome". The search revealed that although the quality of evidence for early rescue surfactant treatment and immediate nasal CPAP assistance as alternatives to prophylactic intubation and surfactant therapy is high, there were no studies investigating lung recruitment procedures before surfactant administration in human infants.

Added value of this study

In this multicentre, randomised, controlled trial, a lung recruitment manoeuvre done before surfactant administration (intubation-recruitment-surfactant-extubation [IN-REC-SUR-E]) did not increase the risk of short-term adverse neonatal outcomes including air-leak syndrome and intraventricular haemorrhage, and decreased the need for mechanical ventilation in the first 72 h of life, compared with a standard IN-SUR-E technique in extremely preterm neonates with RDS.

Implications of all the available evidence

Lung recruitment manoeuvre before early rescue surfactant administration in extremely preterm neonates with RDS appears safe and reduces the need for mechanical ventilation in the first 72 h of life. To our knowledge, this study is the first randomised clinical trial reporting these effects in human preterm infants.

An intubation-surfactant-extubation (IN-SUR-E) procedure achieves this goal: the patient is intubated briefly for the sole purpose of surfactant administration and then extubated to CPAP. Unfortunately, IN-SUR-E is sometimes unsuccessful as some patients cannot be extubated or require reintubation and prolonged mechanical ventilation. Predictors for an unsuccessful IN-SUR-E approach are young gestational age or birthweight, increased severity of respiratory distress syndrome (RDS), and haemodynamic impairment.[2,3] Unsuccessful IN-SUR-E might also be a consequence of de-recruitment of the lung at the time of intubation (and discontinuation of non-invasive support) resulting in less homogeneous surfactant distribution, and therefore reduced surfactant efficacy.[3]

Optimising end-expiratory lung volume before surfactant administration could improve the success rate of IN-SUR-E. Lung recruitment before surfactant administration improved gas exchange and lung function in animal models of lung injury owing to a more homogeneous surfactant distribution within the lungs.[4–6] To date, lung recruitment before surfactant administration has not been studied extensively in preterm infants. Therefore, we aimed to compare the application of a recruitment manoeuvre just before surfactant administration, followed by rapid extubation (intubate-recruit-surfactant-extubate [IN-REC-SUR-E]) with IN-SUR-E alone in spontaneously breathing preterm infants, to establish whether IN-REC-SUR-E decreased the need for mechanical ventilation during the first 72 h of life.

Methods

Study design and participants

The IN-REC-SUR-E trial was a randomised, unblinded, controlled trial done in 35 tertiary neonatal intensive care units in Italy. Infants were eligible for the study if they were born in a tertiary neonatal intensive care unit participating in the trial, had a gestation of 24+0 to 27+6 weeks, were breathing independently with only nasal CPAP for respiratory support, and met nasal CPAP failure criteria during the first 24 h of life. Infants were ineligible if they had severe birth asphyxia or a 5-min Apgar score less than 3, if they required endotracheal intubation in the delivery room for resuscitation or insufficient respiratory drive; were born after prolonged (>21 days) premature rupture of membranes; or if they had a major congenital abnormality, inherited disorder of metabolism, or hydrops fetalis.

The trial protocol was approved by the human research ethics committee in each participating centre.[7] Written and oral information was offered to parents before birth if the mother was at risk for preterm delivery and the infant was likely to be eligible. Written informed consent was obtained from both parents before study enrolment.

Randomisation and masking

Infants were allocated to one of the two treatment groups (1:1) according to the minimisation method, using an interactive web-based electronic system. A study investigator (LB) generated the allocation sequences using the Moses-Oakford method. Randomisation was stratified by centre and gestational age (24+0 to 25+6 weeks or 26+0 to 27+6 weeks). The parents, research staff, and medical team were only aware of study group assignment after randomisation. Procedures

Neonates were stabilised after birth with positive pressure using a neonatal mask and a T-piece system (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). All neonates were started on nasal CPAP

initially and received one or two sustained lung inflation manoeuvres (25 cm H_2O for 10–15 s).[8] Infants that transitioned successfully to spontaneous breathing were transferred to the neonatal intensive care unit on nasal CPAP (6 cm H_2O). The decision to intubate and start invasive mechanical ventilation in the delivery room was in accordance with the American Academy of Paediatrics guidelines.[9]

Nasal CPAP was administered in the neonatal intensive care unit via nasal prongs or nasal mask using the standard method of each participating centre with an initial pressure of 6–7 cm H_2O. Infants received surfactant if they needed a fractional concentration of oxygen in inspired air (FiO_2) of 0·30 or greater to maintain an SpO_2 between 87% to 94% for at least 30 min.[10] Infants were also given surfactant if their clinical status deteriorated rapidly or if they developed respiratory acidosis defined as a pCO_2 more than 65 mm Hg (8·5 kPa) and a pH less than 7·20.

A loading dose of intravenous caffeine citrate (20 mg/kg) was given immediately after admission to the neonatal intensive care unit, followed by a daily maintenance intravenous dose of 5–10 mg/kg. All neonates received pre-intubation medications according to local protocols.

Infants randomly assigned to the IN-REC-SUR-E group were intubated and started on high-frequency oscillatory ventilation using the following ventilator settings: mean airway pressure 8 cm H_2O; frequency 15 Hz; ΔP 15 cm H_2O; and inspiration to expiration ratio of 1:2. Infants underwent an oxygenation guided lung recruitment procedure using stepwise increments then decrements in mean airway pressure to recruit and stabilise collapsed alveoli using the de Jaegere method.[11] Immediately after the recruitment procedure, infants in the IN-REC-SUR-E group received 200 mg/kg of poractant alfa (Chiesi Farmaceutici, Parma, Italy) via a closed administration system in one or two aliquots, while continuing high-frequency oscillatory ventilation.

By contrast, infants allocated to the IN-SUR-E group were intubated and immediately received 200 mg/kg of poractant alfa without previous lung recruitment. Infants were ventilated manually to facilitate surfactant distribution using a T-piece device with a peak inspiratory pressure of 20–22 cm H_2O, a positive end-expiratory pressure of 5–6 cm H_2O, and a respiratory rate of 30–40 breaths per min.

Infants with sufficient respiratory drive were extubated within 30 min after surfactant administration and recommenced on nasal CPAP (6–8 cm H_2O) regardless of group assignment.[12]

Infants in both groups who met the CPAP failure criteria again during the following 24 h received a second dose of surfactant (100 mg/kg of poractant alfa) according to the randomised groups (IN-REC-SUR-E or IN-SUR-E). The indications for mechanical ventilation after IN-REC-SUR-E or IN-SUR-E were poor oxygenation with FiO_2 of greater than 0·40, respiratory acidosis (pCO_2 >65 mm Hg [8·5 kPa] and pH <7·20) or apnoea (more than four episodes of apnoea per h or more than two episodes of apnoea per h requiring ventilation with bag and mask), despite optimal nasal CPAP, nasal intermittent positive pressure ventilation, or bilevel positive airway pressure.

Outcomes

The primary outcome was the need for mechanical ventilation within the first 72 h of life. Infants met the primary outcome if they were not extubated within 30 min after surfactant administration or required reintubation before 72 h of life.

Secondary outcomes included duration of invasive and non-invasive respiratory support, oxygen therapy, and of hospital admission; the number of doses of surfactant; the occurrence of moderate or severe bronchopulmonary dysplasia during hospital admission according to the consensus definition;[13] and mortality. Additional data recorded for each infant included occurrence of: pneumothorax; pulmonary interstitial emphysema; pulmonary haemorrhage; haemodynamically significant patent ductus arteriosus requiring treatment with ibuprofen; grade 3–4 intraventricular haemorrhage;[14] periventricular leukomalacia;[15] worse than grade 2 retinopathy of prematurity;[16] necrotising enterocolitis;[17] sepsis, defined as a positive blood culture or suggestive clinical and laboratory findings leading to treatment with antibiotics for at least 7 days despite absence of a positive blood culture; and use of systemic postnatal steroids.

Statistical analysis

In the absence of published data for the efficacy of a pre-surfactant recruitment manoeuvre on CPAP failure, we based our target of a 20% absolute reduction for sample size estimation on our best estimate of a result likely to effect change in clinical treatment protocols. We powered our study to detect a decrease in the need for subsequent mechanical ventilation during the first 72 h of life from 50% to 30%.[18–20] We calculated that 103 neonates had to be enrolled in each group to detect a significant difference with 80% power at the 0·05 α level using the two-sided Pearson's χ^2 test. 218 patients were randomly assigned to accommodate the risk of enrolling at least 5% of patients judged not meeting inclusion criteria after randomisation. Analyses were done according to the intention-to-treat and per-protocol principles, as suggested by CONSORT guidelines, with the primary outcome assessed in the intention-to-treat population.[21] The intention-to-treat population included all participants assigned to study intervention, and the per-protocol population included all participants who received and completed the study intervention, and met study criteria. For the primary outcome, a log-binomial regression model correcting for the stratification factors of gestational age and study centre was used to estimate the adjusted relative risk

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The main findings of this trial were presented in a platform session at the Pediatric Academic Societies Meeting on April 29, 2019, in Baltimore, MD, USA

(RR). Moreover, the absolute risk reduction and the number-needed-to-treat were calculated. Treatment group and clinical characteristics most likely to be associated with the need for mechanical ventilation (gestational age, sex, antenatal steroids, 5-min Apgar score) were included in a multivariable log-binomial regression analysis to assess their independent role in predicting the clinical outcome.[22] Effect estimates were expressed as RR with 95% CIs. A p value less than 0·05 was considered significant. No adjustments for multiple comparisons were made. Hence, secondary outcome analyses should be interpreted as exploratory.

Statistical analyses were done using Stata software, version 14. An interim-analysis for safety to evaluate the prespecified stopping rules was done at 50% of recruitment by an independent statistician, masked to the treatment allocation. The data and safety monitoring board had unmasked access to all data and discussed the results of the interim analysis with the steering committee in a joint meeting. The steering committee decided on the continuation of the trial and reported to the central ethics committee. This study is registered with ClinicalTrials.gov, NCT02482766.

Role of the funding source

No external funding was received for 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.

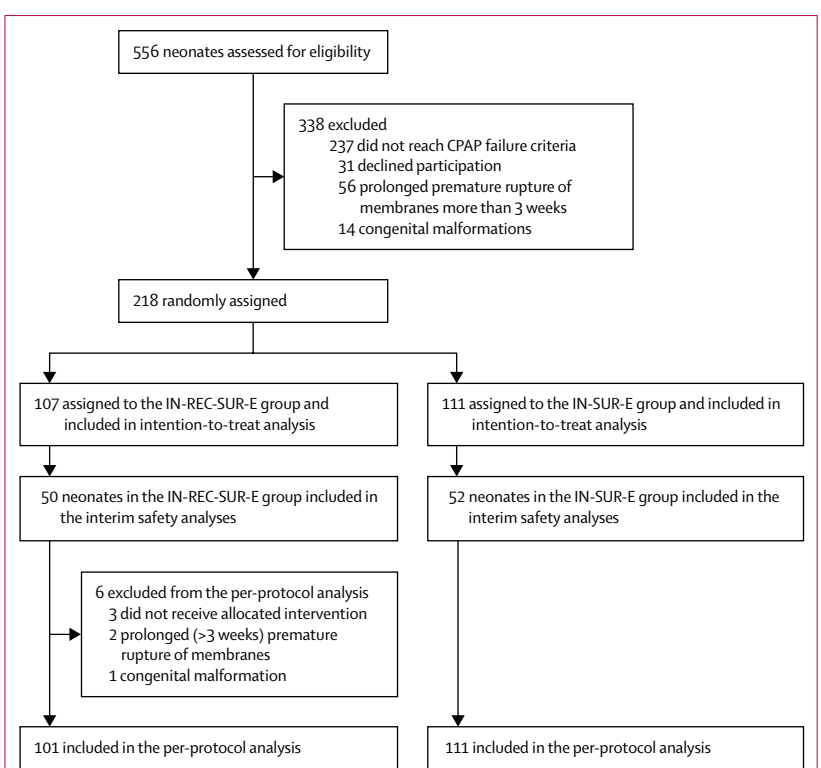

Figure 1: **Trial profile**
IN-SUR-E=intubation-surfactant-extubation. IN-REC-SUR-E=intubate-recruit-surfactant-extubate. CPAP=continuous positive airway pressure.

Results

Of 556 infants assessed for eligibility, 218 were randomly assigned between Nov 12, 2015, and Sept 23, 2018: 107 (49%) infants were assigned to receive IN-REC-SUR-E treatment and 111 (51%) to receive IN-SUR-E treatment. The per-protocol analysis included 212 infants, 101 (47%) in the IN-REC-SUR-E group and 111 (52%) in the IN-SUR-E group (figure 1).

Baseline characteristics of the infants and their mothers are shown in table 1. We observed no differences between IN-REC-SUR-E and IN-SUR-E groups in the proportion of infants receiving specific opioid drugs before intubation for surfactant administration (fentanyl, n=95 [89%] *vs* n=100 [90%]; remifentanil, n=12 [11%] *vs* n=11 [10%]).

The high-frequency oscillatory ventilation recruitment manoeuvre had a median duration of 30 min (IQR 20–45), contributing to an increase in the median hours of life for administration of the first dose of surfactant: 4 h (3–9) in the IN-REC-SUR-E group versus 3 h (2– 5) in the IN-SUR-E group (median difference 1·1, 95% CI 0·42–1·85; p=0·0012). The FiO_2 value at the optimal mean airway pressure (post-recruitment) in the IN-REC-SUR-E infants (0·28, SD 0·09; figure 2) was significantly lower than the FiO_2 at surfactant administration in the IN-SUR-E infants (0·42, SD 0·09, mean difference 0·14, 95% CI 0·11–0·16; p<0·0001). All infants in both groups were extubated within 30 min after surfactant administration. The infants were placed on CPAP (7·0 cm H_2O, SD 0·4 with FiO_2 0·25, SD 0·04 immediately after the IN-REC-SUR-E procedure and 7·0 cm H_2O, SD 0·4 with FiO_2 0·26, SD 0·06 immediately after the IN-SUR-E procedure).

According to the intention-to-treat analysis, the need for mechanical ventilation within the first 72 h of life occurred in 43 (40%) of 107 infants in the IN-REC-SUR-E group and 60 (54%) of 111 infants in the IN-SUR-E group (adjusted RR 0·75, 95% CI 0·57–0·98; p=0·037; table 2). The absolute risk reduction was 14% (95% CI 1–27) with a number needed to treat of 7·2 (3·7–135·0). The indication for mechanical ventilation was mainly acute respiratory failure in both the IN-REC-SUR-E (36 [84%] of 43) and IN-SUR-E (51 [85%] of 60) groups, and secondary to infection (two [5%] of 43 and five [8%] of 60); secondary to patent ductus arteriosus (three [7%] of 43 and three [5%] of 60); and secondary to surgery (two [5%] of 43 and one [2%] of 60).

We observed no differences between the IN-REC-SUR-E and IN-SUR-E groups in the proportion of infants receiving different non-invasive ventilation support strategies after extubation, before starting mechanical ventilation (CPAP, n=76 [71%] *vs* n=85 [76%]; bilevel positive airway pressure, n=15 [14%] *vs* n=14 [13%]; and nasal intermittent positive pressure ventilation, n=16 [15%] *vs* n=12 [11%]). The per-protocol analysis supported a

	IN-SUR-E group (n=111)	IN-REC-SUR-E group (n=107)
Mothers		
Antenatal steroids	100 (90%)	99 (93%)
Vaginal delivery	25 (23%)	26 (24%)
Prolonged premature rupture of membranes	38 (34%)	31 (29%)
Chorioamnionitis	13 (12%)	13 (12%)
Hypertension disorders	32 (29%)	29 (27%)
Infants		
Gestational age, weeks + days	26·3 (1·0)	26·4 (1·0)
24 + 0 to 25 + 6	39 (35%)	34 (32%)
26 + 0 to 27 + 6	72 (65%)	73 (68%)
Birthweight, g	788 (190)	815 (200)
Birthweight in less than tenth percentile for gestational age	20 (18%)	13 (12%)
Singleton birth	82 (74%)	78 (73%)
Male sex	53 (48%)	53 (50%)
5-min Apgar score	8 (7–8)	8 (7–8)
One sustained lung inflation in the delivery room	76 (68%)	76 (71%)
Two sustained lung inflations in the delivery room	35 (32%)	31 (29%)
CPAP in the delivery room, cm H_2O	5·7 (0·5)	5·6 (0·5)
FiO_2 in the delivery room	0·32 (0·11)	0·32 (0·12)
CPAP before surfactant, cm H_2O	6·3 (0·4)	6·2 (0·9)
FiO_2 before surfactant	0·42 (0·09)	0·42 (0·11)

Data are n (%), mean (SD), or median (IQR). IN-SUR-E=intubation-surfactant-extubation. IN-REC-SUR-E=intubate-recruit-surfactant-extubate. CPAP=continuous positive airway pressure. FiO_2=fractional concentration of oxygen in inspired air.

Table 1: **Baseline characteristics**

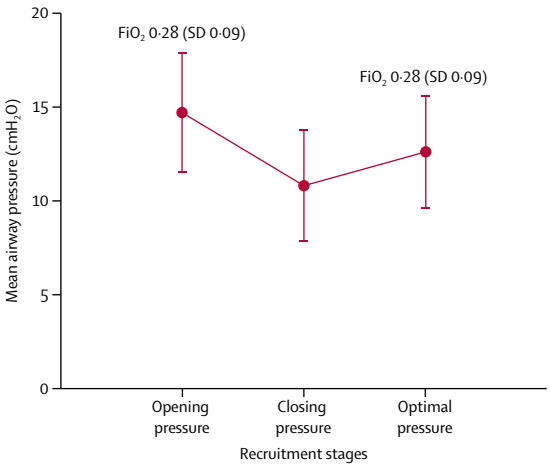

Figure 2: **MAP during the recruitment procedure**
104 infants who received the recruitment procedure were included in this analysis. Starting at 8 cm H_2O, MAP was increased 2 cm H_2O every 2–3 min as long as SpO_2 improved. The FiO_2 was reduced stepwise, keeping SpO_2 within the target range (87–94%). The recruitment was stopped if oxygenation no longer improved or if the FiO_2 was 0·25 or less. The corresponding MAP was the opening pressure. Next, MAP was reduced 1–2 cm H_2O every 2–3 min until SpO_2 deteriorated. The corresponding MAP was the closing pressure. After a second recruitment manoeuvre at opening pressure for 2 min, the optimal pressure was set 2 cm H_2O above the closing pressure. MAP=mean airway pressure. $Fi0_2$=fractional concentration of oxygen in inspired air.

reduced requirement for mechanical ventilation during the first 72 h of life in the IN-REC-SUR-E group (39 [39%] of 101) compared with the IN-SUR-E group (60 [54%] of 111; adjusted RR 0·71, 95% CI 0·53–0·96; p=0·028).

Multivariable analysis on 212 infants (the per-protocol population) showed that older gestational age (RR 0·88, 95% CI 0·78–0·99) and IN-REC-SUR-E treatment (RR 0·73, 0·54–0·98) reduced the need for mechanical ventilation within the first 72 h of life (data not shown) Sex, antenatal steroids, and 5-min Apgar had no significant effect.

Secondary outcomes are reported in table 2. According to the intention-to-treat analysis, in-hospital mortality occurred in 23 (21%) of 107 of the infants in the IN-REC-SUR-E group and in 37 (33%) of 111 infants in the IN-SUR-E group, with no significant difference between the groups (RR 0·64, 95% CI 0·41–1·01; p=0·055; table 2). However, the per-protocol analysis suggested a protective effect of the recruitment procedure on death among infants who received the study interventions (19 [19%] of 101 *vs* 37 [33%] of 111; RR 0·56, 95% CI 0·35–0·91; p=0·020). No significant differences were seen between the two groups in the incidence of moderate to severe bronchopulmonary dysplasia or other morbidities (table 2). The number of infants requiring two doses of surfactant in the IN-REC-SUR-E group (n=44 [41%]) was lower than in the IN-SUR-E group, but this difference was not significant (n=58 [52%]; RR 0·79, 95% CI 0·59–1·05; p=0·10).

No relevant differences were observed between IN-REC-SUR-E and IN-SUR-E treated infants regarding the main causes of death, except for deaths secondary to respiratory failure: nine of these deaths were noted in the IN-REC-SUR-E group (severe RDS [n=5], severe RDS and persistent pulmonary hypertension of the newborn [n=3], and pneumothorax [n=1]), compared with 17 in the IN-SUR-E group (severe RDS [n=7], pulmonary haemorrhage [n=6], severe RDS and persistent pulmonary hypertension of the newborn [n=3], and pulmonary interstitial emphysema [n=1]). Pulmonary haemorrhage was the main cause of death during the first 24 h of life after surfactant treatment in four cases, all of which occurred in the IN-SUR-E group. Deaths occurring in the first 24 h of life from other causes in the IN-REC-SUR-E group were: severe RDS (n=1), severe RDS and persistent pulmonary hypertension of the newborn (n=2), pneumothorax (n=1), infection (n=1), cardiovascular (n=2), and intraventricular haemorrhage (n=1). Deaths occurring in the first 24 h of life from other causes in the IN-SUR-E group were: severe RDS (n=1), severe RDS and persistent pulmonary hypertension of the newborn (n=1), cardiovascular (n=2), acute kidney injury (n=1), and disseminated intravascular coagulation (n=1). However,

	IN-SUR-E group (n=111)	IN-REC-SUR-E group (n=107)	Relative risk (95% CI)	p value
Primary outcome				
Mechanical ventilation in the first 72 h of life	60 (54%)	43 (40%)	..	..
Crude analysis	..	..	0·74 (0·56–0·99)	0·044
Adjusted analysis	..	..	0·75 (0·57–0·98)	0·037
Secondary outcomes				
Two doses of surfactant	58 (52%)	44 (41%)	0·79 (0·59–1·05)	0·10
In-hospital mortality*	37 (33%)	23 (21%)	0·64 (0·41–1·01)	0·055
Invasive respiratory support, days	6 (1–20)	6 (0–20)	..	0·56
Non-invasive respiratory support, days	35 (8–49)	40 (25–53)	..	0·46
Oxygen therapy, days	25 (9–52)	30 (5–63)	..	0·78
Moderate to severe bronchopulmonary dysplasia†	23/75 (31%)	29/86 (34%)	1·09 (0·69–1·71)	0·72
In-hospital stay, days	80 (19–108)	87 (60–107)	..	0·44
Pneumothorax*	7 (6%)	4 (4%)	0·59 (0·18–1·97)	0·39
Pulmonary interstitial emphysema	8 (7%)	4 (4%)	0·52 (0·16–1·67)	0·27
PDAhs	46 (41%)	56 (52%)	1·26 (0·95–1·68)	0·11
Pulmonary haemorrhage	9 (8%)	8 (7%)	0·92 (0·37–2·30)	0·86
Intraventricular haemorrhage worse than grade 2*	17 (15%)	12 (11%)	0·73 (0·37–1·46)	0·38
Periventricular leukomalacia	4 (4%)	10 (9%)	2·59 (0·84–8·02)	0·10
Sepsis‡	63 (57%)	59 (55%)	0·97 (0·77–1·23)	0·80
Necrotising enterocolitis	10 (9%)	11 (10%)	1·13 (0·50–2·55)	0·77
Retinopathy of prematurity worse than grade 2	12 (11%)	15 (14%)	1·30 (0·64–2·64)	0·47
Postnatal steroids	39 (35%)	40 (37%)	1·06 (0·75–1·51)	0·73

Data are expressed as n (%) or median (IQR), unless specified. IN-SUR-E=intubation-surfactant-extubation. IN-REC-SUR-E=intubate-recruit-surfactant-extubate. PDAhs=patent ductus arteriosus, haemodynamically significant, requiring treatment with ibuprofen. *Protocol-defined outcomes reviewed by the data and safety monitoring board for the interim safety analysis. †Defined by the use of supplemental oxygen or nasal continuous positive airway pressure or mechanical ventilation at a post-menstrual age of 36 weeks. Denominators exclude deaths before 36 weeks of post-menstrual age. ‡Diagnosis of clinical sepsis (ie, without confirmation by positive blood culture) as per the clinical protocol was made in ten neonates of the IN-SUR-E group and in six neonates in the IN-REC-SUR-E group.

Table 2: **Effect of IN-REC-SUR-E on primary outcome and secondary outcomes**

the overall incidence of pulmonary haemorrhage was not different between the two groups (table 2). The other causes of death in the IN-REC-SUR-E group were infection (n=8), cardiovascular (n=2), disseminated intravascular coagulation (n=1), intraventricular haemorrhage (n=2), or other causes (n=1). The main causes of death in the IN-SUR-E group were infection (n=9), cardiovascular (n=4), disseminated intravascular coagulation (n=2), intraventricular haemorrhage (n=2), or other cause (n=3).

Discussion

In this trial, a high-frequency oscillatory ventilation lung recruitment manoeuvre done before intubation, surfactant administration, and extubation decreased the need for mechanical ventilation in the first 72 h of life compared with no recruitment manoeuvre in preterm infants born at 24+0 to 27+6 weeks' gestation requiring non-invasive ventilation from birth and meeting CPAP failure criteria. This reduction in the need for mechanical ventilation is likely due to an improved surfactant response after the recruitment procedure, which achieved and maintained an optimal end-expiratory lung volume more effectively than without previous recruitment. Previous studies showed that oxygenation-guided high-frequency oscillatory ventilation recruitment improves end-expiratory lung volume in preterm infants with RDS.[23,24] Moreover, studies suggest that a volume recruitment manoeuvre improves surfactant distribution[4] and that in the absence of a recruitment procedure, surfactant preferentially distributes into underinflated and aerated alveolar areas while rarely reaching collapsed alveolar areas.[5] Animal studies linked the homogeneous distribution of surfactant to the enhancement of its effects on pulmonary gas exchange.[25,26] Similarly, in our trial, the FiO_2 pre-surfactant was significantly lower in the IN-REC-SUR-E treated infants relative to infants receiving IN-SUR-E. The lower pre-surfactant FiO_2 is a consequence of the high mean airway pressure, with correspondingly higher end-expiratory lung volume, obtained after the recruitment manoeuvre relative to no pre-surfactant recruitment. Although the corresponding mean airway pressure values before surfactant administration in the IN-SUR-E group were not reported systematically, they were in the range of 8·8–10·2 cm H_2O during manual ventilation, as per protocol. The efficacy of the recruitment procedure of IN-REC-SUR-E for enhancement of pulmonary gas exchange secondary to more homogeneous surfactant distribution is supported further by the observed lower number of infants requiring two doses of surfactant in the IN-REC-SUR-E group than in the IN-SUR-E group, but this difference was not statistically significant as per table 2.

Our results also underline the inconsistency of the association between lung recruitment and air-leak syndrome. There was no increased frequency of pneumothorax or pulmonary interstitial emphysema in the IN-REC-SUR-E group despite this group being exposed to higher mean airway pressure than was protocolised for manual ventilation with IN-SUR-E. These data are in accordance with the results in surfactant-deficient preterm lambs. Lambs undergoing a recruitment procedure had fewer pneumothoraces than lambs in a low lung volume, no recruitment group.[24] Together, these findings support the value of lung recruitment to optimise gas exchange, improve lung mechanics, and attenuate lung injury during high-frequency oscillatory ventilation. Two previous studies applied a recruitment high-frequency oscillatory ventilation procedure before surfactant administration using a target FiO_2 not exceeding 0·25 and showed that the recruitment did not increase key safety outcomes of air leaks or intraventricular haemorrhage.[11,27] The current study supports these findings.

The similar incidence of moderate to severe bronchopulmonary dysplasia in the two study groups despite the significantly reduced need for mechanical ventilation in

the first 72 h of life in the IN-REC-SUR-E treated infants was a surprising outcome. Duration of mechanical ventilation is a key determinant of bronchopulmonary dysplasia severity, and we thus expected that infants treated with IN-REC-SUR-E would tend to have less severe bronchopulmonary dysplasia.[28] The absence of a difference in this outcome, and in the mean duration of invasive respiratory support, might be off-set by the potentially (and unexpected) lower mortality in the IN-REC-SUR-E than IN-SUR-E groups, mainly evident in the per-protocol analysis; the difference in reduced mortality was not significant in the intention-to-treat analysis. This difference in the intention-to-treat and per-protocol findings might be due to a number of deaths in the IN-REC-SUR-E group that were independent of the procedure: of six patients excluded from the per-protocol analysis, four died during their hospital stay, of which two had not received the recruitment manoeuvre (ie, were not treated according to the experimental group) and two who should not have been randomly assigned (due to prolonged [>3 weeks] premature rupture of membranes). Despite this, the results of the intention-to-treat analysis highlight the potential advantages of the experimental procedure, a result that is supported by the per-protocol analysis.

Our study does have limitations. Although we did a randomised controlled trial, it was unblinded and hence susceptible to treatment bias. Nevertheless, the similarities of the two groups before surfactant administration (in terms of CPAP level and FiO_2) and after surfactant, before starting mechanical ventilation in those infants with unsuccessful non-invasive respiratory support (as additionally outlined by the same proportion of infants receiving different non-invasive ventilation support strategies), suggests that there was no treatment bias and that failure criteria were applied equally between the groups. Second, although 35 centres participated in the trial, only 218 infants were enrolled over almost 3 years, which is only about six infants per centre, a rather low number for a common clinical problem (preterm infants needing surfactant). The study population, however, was made up of extremely preterm neonates (24+0 to 27+6 weeks), with few infants meeting the eligibility criteria (initially managed on CPAP then developing CPAP failure before surfactant administration); some centres might have had high intubation rates in this gestational age group, while others had a lot of success with CPAP alone—ie, we had a very selected population of infants. Thirdly, all the infants in our study received 1–2 sustained lung inflations to 25 cm H_20 for 10–15 s as standard management in the delivery room but a large trial of sustained lung inflation was stopped because of excessive early mortality (at less than 48 h of age) in the treatment group.[29] This issue is important but our trial was designed just before the American Academy of Paediatrics guidelines of 2015,[30] which stated, "we suggest against the routine use of initial sustained inflation (greater than 5 seconds duration) for preterm infants without spontaneous respirations immediately after birth... but a sustained lung inflation may be considered in individual clinical circumstances or research settings". Our study represents a research setting. Importantly, the sustained lung inflation was applied during resuscitation to both study groups and hence does not complicate the interpretation of the IN-REC-SUR-E versus IN-SUR-E comparison.

In conclusion, a lung recruitment manoeuvre before an IN-SUR-E procedure decreased the need for mechanical ventilation in the first 72 h of life in extremely preterm neonates compared with a standard IN-SUR-E technique. Further, adequately powered studies are required to confirm whether IN-REC-SUR-E confers a survival advantage or has benefits for respiratory outcomes over the longer term.

Contributors

GV conceived and designed the study and drafted the manuscript. AL contributed to the literature search. CT, ML, LG, PEV, MRC, ADV, PB, GG, EG, GiG, FS, SM, SDF, CG, AM, HM, FF, LP, CH, SV, GiM, GiP, MV, MDC, PL, LO, DG, RB, AB, CaC, LQ, AC, and LiG contributed to the patient recruitment and randomisation as principal investigators of the participating centres in the study. MT, CA, SC, VD, GN, ViR, VF, FPF, PGM, VV, CP, FP, CM, AS, VS, EB, GM, LI, EC, EM, GA, VR, LGT, KM, SN, AlS, IS, IM, CC, AG, RP, MPR, VC, FT, CaG, LM, MCMS, FeP, IG, VM, and AnS contributed to the patient recruitment and randomisation, and to the data collection as sub-investigators of the participating centres in the study. LB was responsible for the randomisation process. RoP and FrC did the statistical analysis. JJP, FM, CD, MLV, AHvK, ViC, PT, GP, and FC interpreted the data and critically revised the manuscript for important intellectual content and finally approved the version to be published.

Declaration of interests

We declare no competing interests.

Data sharing

After publication of the trial report, formal requests for study data should be made to the corresponding author (GV) using a bespOKe data request form delineating research aims, methods, and the variables needed. Such requests will be considered by the coordinator (GV) and core team (RoP, MLV). If research questions and methods are considered relevant and valid, the data management department of the Policlinico Universitario A Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, will securely transfer the requested, fully anonymised data in the desired format to the party under data transfer agreements. The team will decide about co-authorships, after discussion with the interested party about this. Data requests can be submitted at any time and the data will be accessible for 12 months from publication, with possible extensions considered. The study protocol with amendments, the statistical analysis plan, and informed consent form will be made available.

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