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REGULAR ARTICLE

# Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies

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## ABSTRACT

**Aim:** Preterm infants requiring surfactant replacement have been treated using the INSURE technique, which requires sedation and comprises tracheal intubation, surfactant instillation and extubation. However, minimally invasive surfactant therapy (MIST) does not require sedation, minimises airway injury and avoids placing positive pressure ventilation on an immature lung. This study compared the feasibility of the two techniques and the outcomes in preterm babies with respiratory distress syndrome (RDS).

**Methods:** Preterm infants with RDS prospectively received surfactant via a gastric tube placed in the trachea by direct laryngoscopy with no sedation. Technique-related complications and respiratory outcomes were analysed.

**Results:** We compared 44 patients who received MIST with a historic cohort of 31 patients who received INSURE. This showed no differences in the rate of intubation and mechanical ventilation in the first 72 h, or secondary respiratory outcomes and relevant morbidities, between the babies who received INSURE and those who received MIST. More babies in the MIST group (35%) needed a second dose of surfactant than the INSURE group (6.5%) ($p < 0.0001$).

**Conclusion:** Surfactant administration using MIST, with no sedation, is feasible in preterm infants with RDS. No significant differences in secondary respiratory outcomes were found between the MIST and INSURE techniques.

## INTRODUCTION

Respiratory distress syndrome (RDS) in preterm infants is characterised by respiratory insufficiency, including tachypnoea, cyanosis, retractions and occasionally expiratory grunting and reduced compliance. The cornerstone of the pathophysiology of RDS is surfactant deficiency. Surfactant is one of the principal components of alveolar lining fluid and has tensioactive properties that substantially reduce the tendency for alveoli to collapse during the expiratory phase. Surfactant replacement has been shown to be highly effective in reducing mortality and morbidity (1,2). However, administering surfactant may require sedation, tracheal intubation and mechanical ventilation. Mechanical ventilation has been associated with lung injury and may lead to chronic lung disease, even in infants who have only been ventilated very briefly (3).

Neonatal units are increasingly adopting a gentle approach to ventilator support in preterm infants as standard care (4). Verder et al. (5) introduced the INSURE approach, named after the key three stages in the procedure: INtubation, SURfactant administration and then Extubation as quickly as possible after administration. This new technique aimed to avoid mechanical ventilation and intubation in infants who were initially managed with nasal continuous positive pressure (nCPAP). INSURE has been widely used since its introduction and has been shown to reduce both the need for mechanical ventilation and the incidence of chronic lung disease (6). However, the INSURE technique requires intubation of the trachea, positive pressure ventilation and sedation, and a number of negative side effects have been associated with the technique. For example, INSURE can damage the

### Key notes

- Preterm infants requiring surfactant have been treated using the INSURE technique, which requires sedation and comprises tracheal intubation, surfactant instillation and extubation.
- We compared INSURE with minimally invasive surfactant therapy (MIST), which avoids sedation and mechanical ventilation and minimises invasion of the lower respiratory airways.
- MIST proved a feasible and effective alternative to INSURE, but further research is needed to demonstrate whether MIST improves respiratory outcome in preterm babies.

 

immature lung and can cause pain (7), it can result in stress and airway complications (8), and it can be difficult to extubate infants following the procedure (9–11).

Kribs (12) were the first to describe a technique to administer surfactant during spontaneous breathing in infants with nCPAP. Minimally invasive surfactant therapy (MIST) administers surfactant into the trachea by direct laryngoscopy, via a thin tube with the aid of Magill forceps, while the infant is supported with nCPAP. After surfactant instillation, the tube is immediately removed. MIST can avoid the need for sedation and tracheal intubation and has been shown to reduce the need for mechanical ventilation (13).

The potential benefits of MIST prompted our institution to move from INSURE to MIST as our preferred method for surfactant administration in preterm infants initially stabilised using noninvasive ventilation. The aim of this cohort study was to compare respiratory outcomes from infants receiving surfactant with the MIST technique and compare them with a historical cohort treated with the INSURE technique.

## METHODS

This cohort study compared a prospective cohort of 44 infants treated with MIST with a historical cohort of 31 infants treated with INSURE.

### Mist

Infants treated with the MIST technique were recruited from a regional referral centre at the University and Polytechnic Hospital La Fe, Valencia, Spain, during a 16-month period from April 2011 to August 2012. Patients were eligible if they were born in the hospital with a gestational age of between $24^{+0}$ and $35^{+6}$ weeks and were treated with nCPAP immediately after birth for respiratory distress syndrome attributable to surfactant deficiency. The criterion for surfactant administration was the requirement for supplementary oxygen during the first hour of life to keep arterial partial pressure of oxygen ($p_aO_2$) between 50 to 70 mmHg and/or oxygen saturation ($SpO_2$) measured by pulse oximetry between 88% and 92%. Surfactant was administered through a thin nasogastric tube using an adequately sized laryngoscope and Magill forceps. We systematically carried out chest X-rays prior to surfactant administration to ensure that the oxygen requirement was due to respiratory distress syndrome and not another possible cause of hypoxemia. All babies received prophylactic caffeine (loading dose of 20 mg/Kg iv. followed by 7.5–10 mg/Kg/day) prior to surfactant administration.

We excluded infants from the study if they required intubation in the delivery room for primary resuscitation or had major congenital abnormalities.

Infants undergoing the MIST protocol were premedicated with atropine (0.025 mg/Kg iv.). Then, a thin nasogastric catheter (3.5–4 Fr) was introduced, under direct laryngoscopy, between the vocal cords and into the trachea, with the aid of Magill forceps. A dose of previously warmed 100 mg/kg of surfactant (Curosurf®, Chiesi Farmaceutici S.p.A, Parma, Italy) was then administered over a period of 1–3 minutes. The nasogastric tube was removed immediately after surfactant administration. During the entire procedure, the infants continued to receive noninvasive ventilation (5–6 cm $H_2O$) delivered by an Infant Flow Driver® (Care Fusion, San Diego, CA, USA) via binasal prongs or a nasal mask. The procedure was discontinued if their heart rate dropped below 100 beats per minute or $SpO_2$ dropped below 80%. Infants could receive subsequent doses of surfactant using the same method if they met the MIST criteria again during the following 12 to 24 h. During the procedure, the infant's $SpO_2$ and heart rate were continuously monitored by pulse oximetry (Radical technology, Masimo®, Irvine, CA, USA). Data related to noninvasive ventilation and $FiO_2$ supplementation were collected.

MIST was considered to have failed if the $FiO_2$ requirement was ≥0.6, pH <7.20 and/or pCO2 >65 mmHg or severe work of breathing was present.

The primary endpoint was the percentage of patients requiring mechanical ventilation within the first 72 h after birth. Secondary endpoints were the need for mechanical ventilation at any time, and its duration, the duration of noninvasive ventilation and the need for repeated doses of surfactant. Other outcome criteria were the incidence of patent ductus arteriosus, necrotising enterocolitis, bronchopulmonary dysplasia (defined as ≥28 days of oxygen requirement), intraventricular haemorrhage >grade II, air leak and mortality.

### INSURE

The MIST outcome criteria were compared with a historical control cohort of infants treated with INSURE during a 15-month period immediately before the beginning of the MIST technique. In the INSURE cohort, infants were routinely treated with atropine (0.025 mg/kg iv.) and sedated with fentanyl (4 mcg/kg iv.). Infants were intubated (2.5 size ETT), and surfactant (200 mg/kg) was administered while they received positive pressure ventilation via a T-piece. The criteria for subsequent doses of surfactant, and intubation and mechanical ventilation, were the same as in the MIST protocol. The inclusion and exclusion criteria for both groups were the same and are summarised in Table 1.

Approval for the study was obtained from the institutional ethics committee. Parental consent was obtained prior to enrolling babies in the MIST trial.

### Statistical analysis

Variables of interest are expressed in percentages, means (standard deviation) for normally distributed continuous variables and median (range) for variables not normally distributed, according to the Kolmogorov–Smirnov test. The Fisher's exact test (two-tailed) or Mann–Whitney's *U*-test was used to establish baseline differences between the infants in the MIST and INSURE cohorts. Logistic regression analysis was used to investigate the association between the MIST and INSURE surfactant administration procedures and the need for mechanical ventilation. These were controlled for the effect of potential confounding

  

**Table 1** Baseline characteristics and prenatal risk factors of preterm babies treated with the INSURE (intubation, surfactant, extubation) or MIST (minimal invasive surfactant treatment) techniques

| Variable | INSURE (n = 31) | MIST (n = 45) | p |
|---|---|---|---|
| Gestational age (weeks) | 30.7 (±3) | 30.6 (±2.7) | NS |
| <30 weeks, n (%) | 16 (51%) | 22 (48%) | 0.054 |
| Birthweight (g) | 1576 (±585) | 1516 (±448) | NS |
| Male, n (%) | 22 (71%) | 30 (66%) | NS |
| Apgar 1 min | 6 (4–10)* | 8 (3–10)* | NS |
| Apgar 5 min | 9 (6–10)* | 10 (7–10)* | NS |
| Antenatal steroids, n (%) | 22 (73%) | 40 (90%) | 0.058 |
| C-section, n (%) | 21 (67%) | 30 (66%) | NS |
| Twin delivery, n (%) | 14 (45%) | 21 (46%) | NS |
| Time from birth to surfactant administration (h) | 14.8 (±11.4) | 11.6 (±9.3) | NS |
| $FiO_2$ prior to surfactant administration | 0.36 (±0.07) | 0.35 (±0.1) | NS |

Mean (SD).
*Median (range).

factors: gestational age, birth weight, sex, antenatal steroids, age at administration, oxygen requirement and surfactant dose. $p < 0.05$ were considered statistically significant. Data were analysed using the SPSS package version 19.0 (SPSS®, Chicago, IL, USA) for Windows.

## RESULTS

During the MIST observational period, 342 infants aged between $24^{+0}$ and $35^{+6}$ weeks' gestation were admitted because of respiratory distress. Of these, 38 were intubated during the resuscitation process and 19 had major congenital malformations. The remaining 285 infants were initially managed with noninvasive ventilation. Forty-four infants met the surfactant administration criteria and were treated using the MIST procedure. These 44 MIST infants were compared with a historical cohort of 31 infants treated with the INSURE procedure. This means that data from 75 infants were analysed. The demographic data and prenatal risk factors for the infants in each group are shown in Table 2. There were no significant differences between the baseline characteristics of the two groups. Antenatal steroid use was higher in the MIST group (91%) than the INSURE group (73%) ($p = 0.06$). Surfactant was administered at a postnatal age (mean ± standard deviation) of 11 ± 9 h in the MIST group and 14 ± 11 h in the INSURE group ($p = 0.224$).

### Primary outcome

Fifteen (34%) of the 44 infants in the MIST group were intubated and ventilated after surfactant administration within the first 72 h after birth, compared with eight (26%) of the 31 patients in the INSURE group ($p = 0.44$).

### Secondary outcomes

Data for the secondary outcomes are shown in Table 3. The MIST group infants received statistically more surfactant doses (36%) than those in the INSURE group (6.5%)

**Table 2** Primary and secondary outcomes of preterm infants treated with INSURE (intubation, surfactant, extubation) or MIST (minimal invasive surfactant treatment) techniques

| Variable | INSURE | MIST | p |
|---|---|---|---|
| Surfactant (mg/kg) | 163 (±25) | 102 (±9) | 0.000 |
| Intubation, n (%) | 8 (26%) | 15 (34%) | NS |
| Second dose surfactant, n (%) | 2 (6.5%) | 16 (35.6%) | 0.003 |
| Time (h) from first surfactant to intubation | 19.5 (±14.4) | 28.8 (±18.9) | NS |
| Mechanical ventilation (h) | 150 (40–961)* | 115 (12–1369)* | NS |
| Noninvasive ventilation (h) | 117 (6–2040)* | 102 (9–1447)* | NS |
| Supplemental $O_2$ (h) | 6 (0–2280)* | 18 (3–3144)* | NS |
| Pneumothorax, n (%) | 3 (9.7%) | 3 (6.8%) | NS |
| Patent ductus arteriosus, n (%) | 13 (41%) | 16 (36%) | NS |
| Early onset sepsis (<72 h) | 9 (29%) | 10 (22.7%) | NS |
| Necrotising enterocolitis, n (%) | 3 (9%) | 0 | 0.06 |
| Intraventricular hemorrhage >grade 2 | 0 | 1 (2.3%) | NS |
| Bronchopulmonary displasia, n (%) | 2 (6.5%) | 2 (4.5%) | NS |
| Days of NICU stay, n (%) | 22 (26%) | 20 (24%) | NS |
| Mortality, n (%) | 1 (3.2%) | 2 (4.5%) | NS |

Mean (±SD).
*Median (range).

**Table 3** Comparison of the secondary outcomes of preterm babies treated with surfactant using the INSURE (intubation, surfactant, extubation) or the minimally invasive surfactant therapy

| Variable | INSURE | MIST | p |
|---|---|---|---|
| Surfactant (mg/kg) | 163 (±25) | 102 (±9) | 0.00 |
| Intubation, n (%) | 8 (25) | 15 (33) | NS |
| Second dose surfactant, n (%) | 2 (6.5) | 16 (35.6) | 0.003 |
| Time (h) from birth to intubation | 6.9 (±13.7) | 12.1 (±20.3) | NS |
| Mechanical ventilation (h) | 150 (40–961)* | 115 (12–1369)* | NS |
| Non-invasive ventilation (h) | 117 (6–2040)* | 102 (9–1447)* | NS |
| Supplemental $O_2$ (h) | 6 (0–2280)* | 18 (3–3144)* | NS |
| Pneumothorax, n (%) | 3 (9.7) | 3 (6.8) | NS |
| Patent ductus arteriosus, n (%) | 13 (41) | 16 (36) | NS |
| Early onset sepsis (<72 h) (%) | 9 (29) | 10 (22.7) | NS |
| Necrotizing enterocolitis, n (%) | 3 (9) | 0 | 0.06 |
| Intraventricular hemorrhage > grade 2 (%) | 0 | 1 (2.3) | NS |
| Bronchopulmonary displasia, n (%) | 2 (6.5) | 2 (4.5) | NS |
| Days of NICU stay, n (%) | 22 (26) | 20 (24) | NS |
| Exitus, n (%) | 1 (3.2) | 2 (4.5) | NS |

Mean (±SD).
*Median (range).

($p = 0.00$). Infants in the INSURE group received a dose of surfactant close to 200 mg/kg.

As shown in Table 3, there were no significant differences in the median duration of mechanical ventilation in the subgroup of infants who were ventilated (MIST: 150 h versus INSURE: 115 h) or in the median duration of noninvasive ventilation (MIST: 117 h versus INSURE: 102 h). There were also no significant differences between the two groups regarding any of the other secondary outcomes. There was a trend towards a reduced incidence of necrotising enterocolitis in the MIST group (MIST: 0% versus INSURE: 9%; $p < 0.06$).

### Multiple regression analysis

In a logistic regression model with mechanical ventilation as the dependent variable with no interaction terms, the only two variables independently associated with the need for mechanical ventilation were the presence of a haemodynamically significant patent ductus arteriosus (OR 16.7; 95% Confidence Interval (CI) 2.9–94.8, $p = 0.002$) and the presence of early sepsis (<72 h) (OR 8.5; 95% CI 1.4–49.6, $p = 0.018$).

## DISCUSSION

RDS is a frequent condition affecting preterm infants who often require surfactant replacement therapy. Previous data have shown that the intubation rate in preterm babies with moderate to severe RDS rises with decreasing gestational age and varies between 46% and 80% (14,15). More infants are now initially treated with noninvasive ventilation (4), and intubation solely for the purpose of surfactant administration has been questioned (15). The INSURE procedure aims to shorten the length of time infants are intubated or receive mechanical ventilation (11), but it has not completely avoided either of these outcomes. The MIST procedure aims to minimise stracheal intubation and its associated risks, but there is little data, or published anecdotal evidence regarding its effectiveness (16).

In our study, 66% of the patients in the MIST group and 74% of the patients in the INSURE group did not need intubation after the surfactant was administered. This shows that MIST was as effective as INSURE in avoiding the need for further mechanical ventilation. Göpel reported similar results in a randomised clinical trial that compared the use of MIST for surfactant supplementation with conventional intubation and mechanical ventilation. In that study, the authors reported that infants receiving MIST demonstrated a significant decrease in the need for, and duration of, mechanical ventilation and that the proportion of infants receiving supplemental oxygen on day 28 also decreased (13). Kanmaz et al. (17) reported that infants receiving surfactant via MIST showed a significant reduction in the need for mechanical ventilation 72 h after birth than infants receiving INSURE (30% versus 45%). In comparison, our study showed that the incidence of intubation in the first 72 h was 34% in the MIST group and 26% in the INSURE group. The difference in intubation rates between our study and the Kanmaz study may be due to the different gestational ages of the infants in the two studies. However, our intubation rate is comparable with the 25% reported in the Kribs study, where a cohort of German infants of 24–36 weeks' gestation were treated with a modified INSURE technique that was similar to MIST (20).

The need for a second dose of surfactant in the MIST group has not been reported before and deserves further attention. In our study, around 36% of the infants in the MIST group received a second dose of surfactant. This finding could have occurred because the dose of surfactant in the MIST procedure was 100 mg/kg compared with 200 mg/kg in the INSURE group. However, this is not consistent with previous reports showing good results with a lower surfactant dose (13). A randomised controlled trial by Kanmaz found no difference in the requirement for a second dose of surfactant when it compared MIST and INSURE. Interestingly, in the Kanmaz study, the dose of surfactant was 100 mg/kg in both groups and there was no difference in the proportion of infants needing a second dose (17). Clinicians need a period of training before they are competent enough to use either MIST method or INSURE method to administer surfactant. For this reason, our study is based on trained individuals who implemented the MIST protocol after 12 months' experience. As previously reported, longer training periods lead to better results in terms of avoiding intubation and mechanical ventilation, possibly because the technique is better executed (18). Moreover, this was also reflected in the length of time after birth that surfactant was administered in our study, compared with German Kribs study (18). Finally, another possible factor influencing the need for repeated surfactant dosing could be a more rapid turnover of surfactant in infants who are breathing spontaneously compared with intubated infants (19).

There was little difference in time to intubation after surfactant administration between our two groups, but it tended to be more prolonged in the MIST group. One possible explanation could be that the indications for intubation might have been different between the groups. For example, the indications for intubation in the MIST group may have been influenced by other late-occurring conditions, such as patent ductus arteriosus or apnoea–bradycardia syndrome. In contrast, the decision to intubate in the INSURE group could have been related to factors associated with the procedure itself, for example the sedation given to facilitate the procedure.

We found a significant difference in the proportion of infants treated with antenatal steroids between the MIST and the INSURE groups. When we controlled for this confounding factor using logistic regression, the effect of antenatal steroids was no longer significant. In fact, independent risk factors for intubation were a haemodynamically significant patent ductus arteriosus and the presence of early sepsis, confirming that the method of surfactant administration did not influence the rate of intubation.

Mortality and bronchopulmonary dysplasia were similar in the MIST and INSURE groups, even in the subgroup of

  

infants of 26–28 weeks' gestation (28% versus 20%, respectively, p = 0.636). Our rate of bronchopulmonary dysplasia was comparable with the rates reported in other trials (11,13,20,21). In contrast, the Turkish study by Kanmaz found a lower incidence of bronchopulmonary dysplasia in the MIST group than the INSURE group (10% versus 20%) (17). It is difficult to make comparisons between the different studies due to differences in the gestational ages of the study infants.

Interestingly, we found a trend towards a lower incidence of necrotising enterocolitis in the MIST and INSURE groups (0% versus 3%, respectively, p = 0.06). To our knowledge, this has not been reported in previous studies. Our study was not powered to show an effect in this secondary outcome, but this finding deserves further investigation.

Our study compared a historical cohort against a prospective cohort and has the recognised limitations of this study design. Moreover, because of the retrospective design of the study, we were not able to take into account the number of infants who met the eligibility criteria for the INSURE method. Additionally, we studied a small number of infants. Notwithstanding these limitations, our results support the hypothesis that the MIST procedure for administering surfactant is as safe and effective in reducing the need for intubation as the more invasive INSURE technique. We showed that 67% of study infants managed with the MIST method did not need further intubation. Concern exists about the need for subsequent surfactant dosing and subsequent procedures for surfactant administration. Therefore, it may be necessary to increase the surfactant dose and/or use higher positive end-expiratory pressures when employing the MIST technique. These factors need to be taken into consideration when using this protocol. We plan further appropriately powered studies to test these issues.

## CONFLICT OF INTEREST DECLARATION

The authors of this manuscript declare not having any conflict of interest.

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