Early predictors for INSURE failure in preterm infants with neonatal respiratory distress syndrome: a systematic review

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Short title:

Early predictors for INSURE failure in preterm neonates

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1. Abstract

The INtubation-SURfactant-Extubation (INSURE) procedure is a widely-used surfactant administration method to treat preterm infants with respiratory distress syndrome (RDS) but is not always successful. We conducted a systematic review to identify early predictive factors for failure of this procedure. A systematic literature search was performed until July 2018 in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). Original studies comparing INSURE success with INSURE failure in preterm infants with RDS were included. A predefined data extraction form was used to retrieve data from articles and methodological quality was assessed using the SIGN checklists. Fifteen studies out of 690 identified records met inclusion criteria. Methodological quality varied, only 8 studies performed multivariate analysis. We identified 20 different risk factors in total. Evidence for birth weight as a predictor for INSURE failure was inconsistent, but there was a significant association between decreasing gestational age and failure risk. RDS severity was assessed in multiple ways, using arterial blood gas values, imaging and scoring systems. In conclusion: extremely low birth weight, low gestational age and severe RDS appear to be risk factors for INSURE failure. However, evidence is inconsistent due to important methodological heterogeneity. Therefore, clinical applicability of these results is limited and implies the need for future large cohort studies on this subject.

2. Introduction

Neonatal respiratory distress syndrome (RDS) is caused by lung immaturity and surfactant deficiency in preterm newborns and is an important cause of morbidity and mortality. European guidelines on the management of RDS recommend initiation of nasal Continuous Positive Airway Pressure (nCPAP) from birth combined with early selective surfactant administration [1-5]. Methods have been developed to administer surfactant while avoiding intubation and mechanical ventilation (MV) as much as possible. One of those methods is the INSURE technique (INtubation – SURfactant – Extubation), where infants are intubated and surfactant is administered during a very brief period of MV, after which the infant is extubated again and non-invasive respiratory support is continued [1,6,7].

However, this procedure is not always successful. Some infants cannot be extubated after the procedure, while others need to be reintubated in the following hours or days due to hypoxia or hypercapnia [7]. Often, intubation under those circumstances is more urgent and less well tolerated. This could lead to fluctuations in blood pressure, which has been associated with an increased risk of intracranial haemorrhage [8].

For clinicians, it would be helpful to be able to differentiate in the first hours of life those infants who have a good chance of succeeding the INSURE procedure from those who have a high risk of failing it and, therefore, should preferably be intubated electively for surfactant administration and continued MV.

The aim of this systematic review was to identify early predictive factors for failure of the INSURE procedure in preterm infants with RDS and to present an overview of current existing evidence.

3. Materials and Methods

3.1 Registration

The methods for this review were specified in advance and have been published in a protocol at PROSPERO [9], registration number CRD42015025138.

3.2 Eligibility criteria

Studies were included if they: (1) included preterm infants (< 37 weeks' gestation) with RDS; (2) that received surfactant using the INSURE procedure (INtubation, SURfactant administration, brief MV and planned Extubation within a predefined timeframe); and (3) reported on predictive factors for INSURE failure or success. There was no selected time period or language restriction. Studies that were only reported in abstract form, were excluded.

3.3 Information sources and search

Three structured electronic search strategies, developed by an experienced reviewer (FC), were used, and a literature search was conducted through three medical databases (BDB, FD): MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). The final search was run on July 19th, 2018. Reference lists of the included studies were checked to identify additional studies. We contacted several authors to obtain missing information.

3.4 Study selection

After deleting duplicates, eligibility assessment was performed independently by two reviewers (BDB, FD). Title and abstract of all identified studies were screened for relevance. The remaining records were screened for report eligibility criteria and finally inclusion criteria. Disagreements were resolved by consensus or the third author was consulted for final decision (FC).

3.5 Data collection process

A data extraction form was developed in advance and pilot-tested on three studies. Following information was collected: (1) general information, (2) study characteristics, (3) maternal, (4) neonatal, (5) intervention (including the definition of the INSURE procedure) and (6) outcome characteristics (including the definition of INSURE failure). Data extraction was performed independently by two reviewers (BDB, FD) and discrepancies were resolved by consensus. Multiple publications were collated and assessed as one study.

3.6 Study quality assessment

Methodological quality of the included studies was assessed independently by two authors (BDB, FC) using the SIGN methodology checklist for cohort studies and randomized controlled trials [10]. Following items were evaluated: presence of a clearly focused question; selection, attrition and detection bias; possibility of confounding and statistical analysis. Overall study quality was discussed among the reviewers and expressed as high, acceptable or low according to consensus

3.7 Data synthesis

Our results are presented in accordance with the PRISMA guidelines [11,12]. Risk factors that were statistically significant, in any study, in either univariate analysis, analysis of variance or multivariate analysis (final analysis, p-value <0.05) are presented in summary tables. Continuous outcomes are presented as means (and standard deviation) or medians (and range). Dichotomous outcomes are expressed as odds ratios (OR) or relative risks (RR) with 95% confidence interval (CI).

As stated in our review protocol we intended to statistically combine the results of the individual studies into a meta-analysis where possible. However, due to important study heterogeneity and variability of data in the reported results we were unable to statistically combine the results of the included studies.

4. Results

4.1 Study selection

The search retrieved 1076 records and 29 additional records were identified through hand-searching of reference lists and contacting authors. After adjusting for duplicates, title and abstract of 690 records were screened. Because of irrelevance to the review question 548 records were excluded, while another 85 records were discarded because they met one or more exclusion criteria. Even though we sought to include all eligible articles without language restriction, we had to exclude one additional record because it was written in Persian and we were unable to translate it [13]. The full-text of 56 articles was assessed for eligibility. Finally, fifteen original studies met inclusion criteria [14-28] (Figure 1).

4.2 Study characteristics

The main characteristics and in- and exclusion criteria are summarized in Table 1. The included studies involved a total of 1674 patients with a median sample size of 75 (range 21-322). Inclusion criteria varied. The INSURE procedure was generally well described, but also differed between studies. The (primary) outcome assessed was INSURE failure, for which the definition in the included trials is presented in Table 2. The median INSURE failure rate was 33.3% (range 9.3-52.4).

4.3 Study quality assessment

The methodological quality of the included studies is presented in Figure 2. None of the studies referred to existing evidence supporting their definition of INSURE failure, instead, a new definition was proposed in each study. Eight studies adjusted for possible confounding in a multivariate analysis, although the statistical methods were not always clearly described. After detailed quality assessment we categorized 4 studies as being high quality studies [16,17,19,26], 7 studies as being of acceptable quality [14,18,20-23,28], and 4 studies as having a low methodological quality [15,24,25,27].

4.5 Predictive factors of INSURE failure

4.5.1 Birth Weight (BW)

All studies evaluated BW as a potential predictive factor (Appendix 1). In 10 studies, a significantly lower BW was found in infants who failed INSURE [14,15,17,18,20-24,27], whereas in one study the association was in the opposite direction [26]. Only 7 studies investigated the predictive value of BW in a multivariate analysis (total of 739 patients) [16-19,21,23,26] of which 2 found a significant association. Dani et al. reported that having a BW <750 g increased the risk of INSURE failure significantly with an adjusted RR of 2.77 (95% CI 1.26-6.14) [19]. In the study by Li et al. an adjusted odds ratio (aOR) for INSURE failure of 22 was found for a BW <1150 g, but the confidence interval around that estimate was extremely wide (95% CI 2.124-232.90) [21].

4.5.2 Gestational age (GA)

All but one study investigated GA as a possible predictor for INSURE failure [15] (Appendix 2). In 7 out of the 15 studies, a significantly lower GA was found in infants who failed INSURE as compared to those who succeeded [14,18,20,22,24,27,28]. In multivariate analysis (3 studies, including 514 patients) [16,18,26] a significant association was found in only 2 studies. In Brix's study, each 2-week decrease in GA increased the odds of failing INSURE with a factor 1.8 (95% CI: 1.2-2.8) [16]. In Danaei's study, having a GA of 30 weeks or more, as compared to a GA of less than 30 weeks, decreased the risk of INSURE failure with an aOR of 0.78 (95% CI 0.67-0.91) [18].

4.5.3 Severity of respiratory distress syndrome

Nine factors corresponding with the severity of RDS were identified (Appendix 3).

4.5.3.1 Arterial blood gas analysis

Seven studies evaluated *partial carbon dioxide pressure (pCO_2) prior to INSURE procedure* [14,16,17,19-21,27]. In 4 of those studies, a significantly higher pCO_2 prior to INSURE was found in infants who failed as compared to infants who succeeded INSURE [17,19-21]. Three studies performed a multivariate analysis (including 502 patients) with pCO_2 prior to INSURE procedure as co-variate [16,17,21]. In the study by Cherif et al, a pCO_2 of >50 mmHg increased the odds of

failure significantly with a factor 1.82 (95% CI 1.76-90.56), and in the study by Li et al the aOR for a pCO_2 value above 54 mmHg prior to INSURE to fail the procedure was 9.63 (95% CI 1.96-44.74) [17,21].

Six studies reported on *partial oxygen pressure (pO_2) before INSURE procedure* [16,17,19-21,27]. In only 1 study, a significantly lower pO_2 prior to INSURE was found in infants who failed the procedure [21]. The one study that used pO_2 prior to INSURE as a co-variate in a multivariate analysis, did not find a significant association [16].

Six studies evaluated *fractional inspired oxygen concentration (FiO_2) before INSURE procedure* [14-16,19,20,25], which was significantly higher in infants who failed as compared to infants who succeeded INSURE in 3 studies [15, 19, 20]. In multivariate analysis (362 patients), a significant association was found in only one low quality study [15].

Five studies investigated *arterial-to-alveolar partial oxygen pressure ratio (a/ApO_2) prior to INSURE procedure* as an early predictor of INSURE failure [16,17,19,21,26]. In 3 of those studies the a/A-ratio was significantly lower in infants who failed INSURE [17,19,21]. Multivariate analyses (4 studies including 534 patients) are inconsistent. However, both in the cut-off points that were used in the different studies (varying between 0.44 and 0.18) as well as in their results [16,17,19,26]. The *partial arterial oxygen tension to inspired oxygen fraction ratio (paO_2/FiO_2)* was evaluated in 2 studies which both found a statistically significant association with treatment failure in multivariate analyses [19,21]. In Dani's study a paO_2/FiO_2 <218 increased the odds of failure with a factor 1.88 (95% CI 1.26-2.80), whereas in Li's study the aOR of a paO_2/FiO_2 <195 for INSURE failure was 6.57 (95% CI 1.02-42.00). *Oxygenation index* (OI) was evaluated in only 1 study and the analysis was not adjusted for possible confounding [28].

4.5.3.2 Clinical and radiological diagnosis

Four studies reported on a clinical RDS severity score, using either the Silverman-Andersen score [22,26], or an unreferenced scoring system [18,20]. In 3 of those studies, the RDS score was significantly associated with INSURE failure in unadjusted analyses [18,20,22]. Only one study confirmed this association after adjusting for confounders and reported an increase in failure with an odds ratio of 6.31 (95% CI 2.07-19.9) [18]. However, the exact definition of the variable as it was introduced in the multivariate model was unclear.

The *severity of RDS on chest X-ray* was evaluated in 3 studies [15,17,20]. All studies used the same classification system of mild, moderate or severe radiological RDS as described by Kero et al. in 1979 [29]. A statistically significant association was found between the presence of severe radiological RDS and the risk of INSURE failure in 2 studies [15,17].

4.5.4 Other early predictive factors

Ten other factors were evaluated as potential predictive factors for INSURE failure. A summary of these data is provided in Table 3. Noteworthy, a *serum haemoglobin level <14 g/dL prior to INSURE* was found to be significantly associated with failure in 1 out of 2 studies [16,17]. Furthermore, Ognean et al. [25] reported a significant association with pregnancy complications. In the other included studies, different types of pregnancy complications (such as hypertension, pre-eclampsia and diabetes) were evaluated as predictive factors, but were never found to be significantly associated with INSURE failure [16-23,25].

5. Discussion

5.1 Summary of evidence

This is the first systematic review to present an overview of early clinical factors predicting failure of the INSURE procedure performed in preterms with RDS. We identified 21 possible predictors in 15 original studies. Birth weight, gestational age and RDS severity were the most frequently assessed factors.

Although in most studies, average birth weight was lower in infants who failed INSURE, the evidence for birth weight as an independent predictor for INSURE failure was inconsistent. Multivariate analysis in Brix's study even found a potentially protective effect of an extremely low birth weight (<1000 g), although not statistically significant [16]. There is no obvious explanation for this unexpected finding. Study design differed concerning inclusion criteria, indication for INSURE and use of sedative medication. In addition, several study groups used a different cut-off value for the ELBW group, which complicates direct comparison of these results. Although based on only 5 studies, being small for gestational age does not appear to be an independent risk factor of INSURE failure. Thus, although there is some suggestion that an extremely low birth weight might be associated with an increased risk of INSURE failure, the evidence is weakened by inconsistency and does not allow determining a safe cut-off value or making clear recommendations for clinical practice.

In many of the included studies, the average gestational age was significantly lower in infants who failed INSURE, suggesting that the degree of immaturity is a contributing factor. According to Brix's study, in which adjustments were made for possible confounding, each 2-week decrease in gestational age increases the odds of INSURE failure with a factor 1.8 [16]. Particularly infants with a GA of less than 26 weeks had a much higher risk of INSURE failure with an adjusted OR of almost 10 as compared to infants with a GA of 30-31 weeks. These data suggest that we probably should be more cautious when considering an INSURE in extremely low gestational age infants.

Assessing RDS severity in the first hours after birth could be another potentially useful way to select infants for either INSURE or intubation and continued MV. The question is which parameter to use, and at which cut-off point. The use of pCO_2 is supported by 2 studies showing that hypercapnia (pCO_2 >50-55 mmHg) prior to INSURE is indicative of a higher risk of failure. Among the various indices of oxygenation that have been investigated, the arterial-to-alveolar oxygen tension ratio (a/A-ratio) has been studied the most. However, results are difficult to apply in clinical practice because of inconsistency between studies both regarding the cut-off value that was used (between 0.18 and 0.44), as well as in their findings. In addition, calculating an a/A-ratio is rather complicated requiring both pO_2 and pCO_2. The paO_2/FiO_2-ratio, which is easier to calculate, was also found to be associated with the risk of INSURE failure, although the applicability in daily practice is again questionable. Applying the cut-off values that were used in the 2 studies (i.e. <195 and <218), would mean that e.g. an infant with a pO_2 of 70 mmHg would be at increased risk of failing INSURE if the FiO_2 prior to INSURE exceeds 0.32 to 0.36, which is only slightly above the level of indication for surfactant therapy.

The remaining RDS severity indices were analysed using heterogeneous methodologies. Other composite indices, that are mostly used to quantify the severity of (chronic) respiratory failure, have also been considered to predict respiratory failure in early stages of RDS and even to guide medical interventions [30-33]. Amongst them are the OI, A-a DO_2 (alveolar-arterial oxygen difference) and paO_2/FiO_2. However, they were poorly investigated in general.
Thus, until today, available studies do not support the use of any respiratory index or clinical score for RDS severity to reliably select infants in the first hours of life for either INSURE or intubation and continued MV.

Interestingly, a low serum haemoglobin level was found to be significantly associated with a higher risk of INSURE failure [16,17]. We could not find a clear underlying mechanism for this result. Brix et al. speculated that this might be related to the insufficient oxygen delivery to the peripheral tissues leading to lactic acidosis and decreasing pH, but he failed to show an association between high lactate or low pH and INSURE failure [16]. Lactate has not been investigated in any of the other included studies. Differences in pH before INSURE procedure were addressed in five of the included studies but none of them found a significant association with INSURE failure [14,16,17,20,27]. The association with a low serum haemoglobin deserves more attention in future research.

Evidently, factors related to the procedure itself also play an important role in the success or failure of the INSURE procedure. One such factor is the type of exogenous surfactant and the dosing regimen that was used. Current guidelines recommend the use of poractant alfa at a a dose of 200 mg/kg [1]. Except for some studies using beractant, most of the included studies used this type of surfactant at a dose of 100-200 mg/kg (Table 1). Another factor of interest is the use of sedative medication, with the possible side effect of respiratory depression. However, data on sedation was lacking for most of the included studies (Table 1), making it impossible to make any statement on this topic.

European guidelines on RDS treatment now state that Minimally Invasive Surfactant Treatment (MIST) [34] or Less Invasive Surfactant Administration (LISA) [35] is the preferred mode of surfactant administration [1]. This is also stated in the United Kingdom national consensus [36]. With this technique, which has a lot of similarities with INSURE, surfactant is administered through a thin catheter which is introduced into the trachea, while maintaining spontaneous breathing and avoiding intubation and MV. More recent randomised controlled trials and meta-analyses suggest that MIST/LISA is superior to INSURE in terms of a composite outcome of death or bronchopulmonary dysplasia (BPD) [37]. However, despite promising results from randomized controlled trials [38-42], the treatment failure rate of MIST/LISA remains considerable. Results on failure rate are variable, taking into account more recent literature, ranging from 30% [43] to 47% [39] (median INSURE failure rate of 33.3% in this review). Thus far, there is only very few data on predictive factors for MIST/LISA failure. In one study comparing infants who failed versus those who succeeded MIST/LISA procedure, gestational age was the only early factor found to be significantly associated with failure in univariate analysis [44]. This observation was confirmed in a more recent retrospective cohort study, where MIST failure increased with decreasing gestational age. Other predictive factors for MIST failure were an elevated CRP value, absence of antenatal steroids and surfactant dose [43]. Most likely, the early risk factors identified in our systematic review for INSURE failure can be considered as

possible predictors of MIST/LISA failure as well, although this needs to be confirmed in future studies.

5. 2 Strengths and limitations

A comprehensive search was performed, in the large databases and in additional sources, thereby minimizing the risk of publication bias. All steps of the review process were performed by two reviewers independently. We evaluated all potential predictive factors without limitations and thus, were able to present a complete overview of the clinical predictors for INSURE failure that have been studied.

Our review has several limitations. First, we had to exclude one possibly eligible study because of translation issues [13]. Secondly, the quality of studies differed substantially, with only half of the studies providing a multivariate analysis. And third, there was significant methodological heterogeneity between studies. As expected, inclusion criteria for gestational age and birth weight, the criteria for INSURE, the procedure itself and outcome definitions varied across studies. There was also considerable heterogeneity between studies regarding indices for RDS severity, classification of these predictors and cut-off values per index. As a result, we could not conduct a meta-analysis.

5. 3 Implications for practice

Currently available evidence does not provide us with clear-cut decision tools that allow us to select preterm infants with RDS in the first hour of life either for surfactant administration via INSURE or for intubation and continued MV. The results are inconsistent, partly related to heterogeneity across studies, and therefore difficult to apply in clinical practice.
There is some evidence that an extremely low birth weight (<750-1000 grams), a lower gestational age, or more severe RDS lead to a higher risk of INSURE failure. However, based on the results from this systematic review, it was impossible to construct an accurate clinical predictive model.

5. 4 Implications for future research

There is need for large well-conducted cohort studies that evaluate possible early predictive factors for INSURE failure. They should investigate well defined predictors for RDS, such as early clinical factors or (new) biological markers that can be tested for in the first hours of life. Outcomes should be clearly defined and used in similarly across studies, taking into account multiple confounders using multivariate analysis. In addition, research should be done in a patient population that is representative of the current NICU population (preterms often treated with antenatal steroids and relatively mild RDS). In that way, quantitative synthesis of the size of effect of the individual risk factors becomes possible, more accurate and thus, applicable for every day clinical practice.

5. 5 Conclusion

We presented a complete overview of early predictive factors for INSURE failure. Extremely low birth weight, low gestational age and severe RDS appear to be important risk factors for INSURE failure. However, evidence is inconsistent due to important methodological heterogeneity across

studies. Therefore, clinical applicability of these results is limited at the moment and implies the need for future large cohort studies on this subject.

6. Appendices

Appendix 1. Studies reporting on birth weight as possible predictor for INSURE failure

Appendix 2. Studies reporting on gestational age as possible predictor for INSURE failure

Appendix 3. Summary of the results on different indices for RDS severity as possible predictors for INSURE failure

7. Statements

7.1. Acknowledgement

Not applicable.

7.2. Statement of Ethics

The authors have no ethical conflicts to disclose.

7.3. Disclosure Statement

The authors have no financial or conflicts of interest to declare.

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7.5. Author Contributions

All authors contributed substantially to the conceptualization and design of this systematic review. BDB drafted the initial manuscript. FD and FC reviewed and edited the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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9. Figure Legends

Figure 1. Flow diagram of the study selection process.

Figure 2. Quality assessment of the included studies.

10. Table Legends

Table 1. Characteristics of the included studies

Table 2. Outcome definitions in the included studies

Table 3. Summary of the results on other possible early predictive factors for INSURE failure