Early Predictors for INTubation-SURfactant-Extubation Failure in Preterm Infants with Neonatal Respiratory Distress Syndrome: A Systematic Review

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Keywords

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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. 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 (BW) as a predictor for INSURE failure was inconsistent, but there was a significant association between decreasing gestational age (GA) and failure risk. RDS severity was assessed in multiple ways, using arterial blood gas values, imaging, and scoring systems. In conclusion, extremely

low BW, low GA, 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.

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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 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 INTubation-SURfactant-Extubation (INSURE) technique, where infants are intubated and surfactant is administered during a very brief period of MV, after which the infant is extubated again and noninvasive 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 hemorrhage [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.

Materials and Methods

Registration

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

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.

Information Sources and Search

Three structured electronic search strategies, developed by an experienced reviewer (F.C.), were used, and a literature search was conducted through 3 medical databases (B.D.B., F.D.): MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The final search was run on July 19, 2018. Reference lists of the included studies were checked to identify additional studies. We contacted several authors to obtain missing information.

Study Selection

After deleting duplicates, eligibility assessment was performed independently by 2 reviewers (B.D.B., F.D.). 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 (F.C.).

Data Collection Process

A data extraction form was developed in advance and pilot-tested on 3 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 2 reviewers (B.D.B., F.D.), and discrepancies were resolved by consensus. Multiple publications were collated and assessed as one study.

Study Quality Assessment

Methodological quality of the included studies was assessed independently by 2 authors (B.D.B., F.C.) 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.

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 SD) or medians (and range). Dichotomous outcomes are expressed as ORs or relative risks with 95% 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.

Results

Study Selection

The search retrieved 1,076 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] (Fig. 1).

Study Characteristics

The main characteristics and in- and exclusion criteria are summarized in Table 1. The included studies involved a total of 1,674 patients with a median sample size of 75 (range 21–322). Inclusion criteria varied. The INSURE procedure was not only generally well described but also differed between studies. The (primary) outcome as-

Fig. 1. Flow diagram of the study selection process. CENTRAL, Cochrane Central Register of Controlled Trials.

sessed 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).

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].

Predictive Factors of INSURE Failure

Birth Weight

All studies evaluated BW as a potential predictive factor (online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000501654). 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. [19] reported that having a BW <750 g increased the risk of INSURE failure significantly with an adjusted relative risk of 2.77 (95% CI 1.26–6.14). In the study by Li et al. [21], an adjusted OR (aOR) for INSURE failure of 22 was found for a BW <1,150 g, but the CI around that estimate was extremely wide (95% CI 2.124–232.90).

Gestational Age

All but one study investigated gestational age (GA) as a possible predictor for INSURE failure [15] (online suppl. 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 <30 weeks, decreased the risk of INSURE failure with an aOR of 0.78 (95% CI 0.67–0.91) [18].

Severity of RDS

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

Arterial Blood Gas Analysis: Seven studies evaluated *partial carbon dioxide pressure (pCO₂) prior to INSURE procedure* [14, 16, 17, 19–21, 27]. In 4 of those studies, a significantly higher pCO₂ prior to INSURE was found

Table 1. Characteristics of the included studies

Author, year	Country	Time of study	Number of patients	Study design	Quality assessment	Study population	Criteria for INSURE	Type of surfactant, dose	Cointerventions	Duration of procedure
Ancora et al. [14], 2010	Italy	2002–2008	60	Retrospective cohort study	Acceptable	GA: <32 weeks BW: <1,500 g	FiO ₂ >0.40 for >30 min on nCPAP	Poractant Alfa 200 mg/kg	Caffeine citrate Pain management (atropine + fentanyl)	2–5 min
Azzabi et al. [15], 2016	Tunisia	2012–2013	40	Prospective cohort study	Low	GA: 27–35 weeks RDS: clinical signs and chest X-ray	FiO ₂ >0.35	Porcine-derived surfactant 100–200 mg/kg	Not reported	Not reported
Brix et al. [16], 2014	Denmark	1998–2010	322	Retrospective cohort study	High	Inborn GA: <32 weeks	<30 w: a/A pO ₂ ratio <0.36 ≥30 w: a/A pO ₂ ratio <0.22	Poractant Alfa 200 mg/kg	Theophyllamine or caffeine citrate Preintubation medication (atropine + suxametonium + thiomebumal + morphine)	Maximum 2 h
Cherif et al. [17], 2008	Tunisia	2004–2007	109	Retrospective cohort study	High	Spontaneous breathing at birth RDS	a/A pO ₂ ratio ≤0.25	Poractant Alfa 200 mg/kg	Caffeine citrate Morphine	Usually within 10 min
Danaei et al. [18], 2017	Iran	2011–2016	192	Retrospective cohort study	Acceptable	Inborn, hospitalized for up to 48 h GA: 26–36 weeks BW: 500–3,500 g RDS: medical history, clinical findings, and chest X-ray	Not reported	Beractant 100 mg/kg	Not reported	Usually within 10 min
Dani et al. [19], 2010	Italy	2005–2008	75	Prospective cohort study	High	Inborn GA: <30 weeks RDS: clinical signs and chest X-ray	FiO ₂ >0.30	Poractant Alfa 200 mg/kg	Not reported	Usually within 5 min
Gharehbaghi et al. [20], 2014	Iran	2012	147	Prospective cohort study	Acceptable	GA: preterm infants Spontaneous breathing at birth	FiO ₂ >0.30 CPAP with PEEP >5 cm H ₂ O	Not reported	Not reported	Maximum 1 h
Li et al. [21], 2014	China	2010–2013	71	Retrospective cohort study	Acceptable	Inborn GA: <32 weeks RDS	Not reported	Porcine derived surfactant 100–120 mg/kg	Not reported	2 min

Table 1 (continued)

Author, year	Country	Time of study	Number of patients	Study design	Quality assessment	Study population	Criteria for INSURE	Type of surfactant, dose	Cointerventions	Duration of procedure
Morales-Barquet et al. [22], 2017	Mexico	2011–2014	183	Retrospective cohort study	Acceptable	Inborn BW: <1,500 g RDS: clinical or radiological suspicion	FiO ₂ >0.40 with- in 60 min after start nCPAP PEEP 5–6 cm H ₂ O	Poractant alfa 200 mg/kg	Not reported	Maximum 1 h Usually within 5 min
Najafian et al. [23], 2014	Iran	2009–2010	45	Prospective cohort study	Acceptable	Inborn, hospitalized for up to 48 h BW: <1,500 g RDS: medical history, clinical findings and chest X-ray	Not reported	Beractant 100 mg/kg	Not reported	Maximum 2 h
Naseh and Yekta [24], 2014	Iran	Not reported	242	Retrospective cohort study	Low	GA: <37 weeks RDS: clinical signs and chest X-ray	FiO ₂ >0.40 RDS score >6 RDS diagnosis at 30 min of age	Poractant alfa or Beractant 100 mg/kg	Not reported	2–3 min
Ognean et al. [25], 2016	Romania	2010–2011	57	Retrospective cohort study	Low	GA: ≤32 weeks	Decided by physicians based on RDS severity	Poractant alfa 100–200 mg/kg	Not reported	Not reported
Tagare et al. [26], 2014	India	2008–2009	28	Prospective cohort study	High	GA: <37 weeks	FiO ₂ >0.40 for >30 min on CPAP	Beractant 100 mg/kg	Xanthine derivatives as needed	5 min
Talosi et al. [27], 2014	Hungary	2012–2014	82	Unclear	Low	GA: prematures	Prophylactic during resuscitation Deterioration of the clinical condition	Poractant alfa 200 mg/kg	Naluphin Caffeine	Not reported
Tooley and Dyke [28], 2003	UK	1997–1999	21	Randomized controlled trial	Acceptable	Inborn GA: 25–28 6/7 weeks	Prophylactic at birth	Pumactant 100 mg	Caffeine base	Maximum 1 h

GA, gestational age; BW, birth weight; (n)CPAP, (nasal) continuous positive airway pressure; RDS, respiratory distress syndrome; PEEP, positive end expiratory pressure; FiO₂, fractional inspired oxygen concentration, a/A pO₂ ratio, ratio of arterial to alveolar partial oxygen tension; INSURE, Intubation-SURfactant-Extubation.

Table 2. Outcome definitions in the included studies

Author, year	INSURE failure rate, %	Criteria for INSURE failure	Criteria for mechanical ventilation	Notes
Ancora et al. [14], 2010	33.3	Need for MV within 7 days Absence of respiratory drive	FiO ₂ : >0.40 ABG: pH <7.20, pCO ₂ >70 mm Hg Apnea: 4 episodes per hour or >2 episodes requiring bag and mask ventilation nCPAP pressure: PEEP 6 cm H ₂ O	
Azzabi et al. [15], 2016	32.5	Need for MV within 72 h	FiO ₂ : >0.45 Progressive respiratory failure	
Brix et al. [16], 2014	24.8	Need for MV within 72 h	Acute respiratory insufficiency ABG: pH <7.20, a/A pO ₂ ratio <0.15	Neonates mechanically ventilated during surfactant administration (>2 h): Short MV (≤24 h) Long MV (>24 h)
Cherif et al. [17], 2008	32.1	Need for MV within 72 h	FiO ₂ : >0.60 ABG: pH <7.20, pCO ₂ >65 mm Hg, a/A pO ₂ ratio <0.15, BE >10 mmol not responsive to treatment Apnea: >3 episodes in 3 h, unresponsive to stimulation and caffeine treatment	
Danaei et al. [18], 2017	41.1	Need for MV within 24 h	FiO ₂ : >0.40 ABG: pH <7.20, pO ₂ <50 mm Hg, pCO ₂ >60 mm Hg Apnea: recurrent Target saturation: >85%	
Dani et al. [19], 2010	9.3	Need for MV within 72 h	FiO ₂ : >0.50 ABG: pH <7.20, pO ₂ <50 mm Hg, pCO ₂ >65 mm Hg Apnea: Frequent episodes requiring repeated stimulation or bag-and-mask ventilation Target saturation: 85–95% nCPAP pressure: 5–6 cm H ₂ O	
Gharehbaghi et al. [20], 2014	30.6	Need for MV within 72 h No extubation after 1 h	FiO ₂ : >0.50 ABG: pH <7.20, pO ₂ <50 mm Hg, pCO ₂ >65 mm Hg Apnea: >4 episodes per h Target saturation: 88–92%	
Li et al. [21], 2014	40.8	Need for MV within 72 h	FiO ₂ : >0.60 ABG: pH <7.20, pO ₂ <60 mm Hg, pCO ₂ >60 mm Hg Apnea: frequent and severe (requiring PPV) No improvement or deterioration of the condition after applying nCPAP	
Morales-Barquet et al. [22], 2017	38.8	Need for MV within 72 h	FiO ₂ : >0.60 ABG: pH <7.20, pO ₂ <0.35, pCO ₂ >65 mm Hg Apnea: >6 episodes in 6–12 h, 2 requiring PPV in 12 h Target saturation: >88% nCPAP pressure: 5–6 cmH ₂ O Severe RDS (Silverman-Andersen classification >5 points) Need for second dose of surfactant	

Table 2 (continued)

Author, year	INSURE failure rate, %	Criteria for INSURE failure	Criteria for mechanical ventilation	Notes
Najafian et al. [23], 2014	35.6	Need for MV	ABG: pH <7.20, pCO ₂ >60 mm Hg, pO ₂ <50 mm Hg Target saturation: ≥85% nCPAP pressure: PEEP 6 cm H ₂ O	Timing of outcome assessment is not reported
Naseh and Yekta [24], 2014	26.0%	Need for MV	Signs of RD ABG: pH <7.20, pCO ₂ >60 mm Hg, pO ₂ <50 mm Hg Target saturation: ≥85% No improvement on NIPPV (rate 20/min, PIP 14 cm H ₂ O)	Timing of outcome assessment is not reported
Ognean et al. [25], 2016	45.6%	Need for MV within 72 h	Not reported	
Tagare et al. [26], 2014	42.9%	Need for MV within 72 h	FiO ₂ : >0.60 Apnea: >2 episodes requiring PPV nCPAP pressure: PEEP 8 cm H ₂ O Worsening SA scores Shock	
Talosi et al. [27], 2014	25.6%	Need for MV within 7 days Absence of respiratory drive	Deterioration of clinical condition (grunting, chest retractions, cyanosis)	67% intubated at birth (no clear indications reported)
Tooley et al. [28], 2003	52.4%	Need for MV within 48 h (= unsuccessful extubation)	FiO ₂ : >0.70 ABG: pH <7.20, pO ₂ <45 mm Hg Significant apnea nCPAP pressure: max 9 cm H ₂ O	Separate group for neonates that were not extubated

MV, mechanical ventilation; CPAP, continuous positive airway pressure; PEEP, positive end expiratory pressure; ABG, arterial blood gas; PPV, positive pressure ventilation; BE, base excess; RDS, respiratory distress syndrome; INSURE, INTubation-SURfactant-Extubation; nCPAP, nasal continuous positive airway pressure.

in infants who failed as compared to infants who succeeded INSURE [17, 19–21]. Three studies performed a multivariate analysis (including 502 patients) with pCO₂ prior to INSURE procedure as covariate [16, 17, 21]. In the study by Cherif et al. [17], a pCO₂ of >50 mm Hg 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. [21], the aOR for a pCO₂ value above 54 mm Hg prior to INSURE to fail the procedure was 9.63 (95% CI 1.96–44.74).

Six studies reported on *partial oxygen pressure (pO₂) before INSURE procedure* [16, 17, 19–21, 27]. In only 1 study, a significantly lower pO₂ prior to INSURE was found in infants who failed the procedure [21]. The one study that used pO₂ prior to INSURE as a covariate in a multivariate analysis, did not find a significant association [16].

Six studies evaluated *fractional inspired oxygen concentration (FiO₂) 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 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, both in the cutoff 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 (paO₂) to FiO₂ ratio* was evaluated in 2 studies,

	Aim of study	Group comparability	Participation rate	Attrition bias	Clearly defined outcome	Blinded assessor	Assessment of predictive factors	Assessment of outcome	Confounders	CI	Overall risk of bias
Ancora, 2010	+	+	+	+	+	+	+	+	+	+	+
Azzabi, 2016	+	+	+	+	+	+	+	+	+	+	+
Brix, 2014	+	+	+	+	+	+	+	+	+	+	+
Cherif, 2008	+	+	+	+	+	+	+	+	+	+	+
Danaei, 2017	+	+	+	+	+	+	+	+	+	+	+
Dani, 2010	+	+	+	+	+	+	+	+	+	+	+
Gharehbaghi, 2014	+	+	+	+	+	+	+	+	+	+	+
Li, 2014	+	+	+	+	+	+	+	+	+	+	+
Morales-Barquet, 2017	+	+	+	+	+	+	+	+	+	+	+
Najafian, 2014	+	+	+	+	+	+	+	+	+	+	+
Naseh, 2014	+	+	+	+	+	+	+	+	+	+	+
Ognean, 2016	+	+	+	+	+	+	+	+	+	+	+
Tagare, 2014	+	+	+	+	+	+	+	+	+	+	+
Talosi, 2014	+	+	+	+	+	+	+	+	+	+	+
Tooley, 2003	+	+	+	+	+	+	+	+	+	+	+

Fig. 2. Quality assessment of the included studies.

which both found a statistically significant association with treatment failure in multivariate analyses [19, 21]. In Dani's study, a $\text{paO}_2/\text{FiO}_2 < 218$ 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 $\text{paO}_2/\text{FiO}_2 < 195$ for INSURE failure was 6.57 (95% CI 1.02–42.00). *Oxygenation index* was evaluated in only 1 study, and the analysis was not adjusted for possible confounding [28].

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 OR 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 classifica-

tion system of mild, moderate, or severe radiological RDS as described by Kero and Mäkinen [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].

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 hemoglobin level* $< 14 \text{ g/dL}$ 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, preeclampsia, and diabetes) were evaluated as predictive factors, but were never found to be significantly associated with INSURE failure [16–23, 25].

Discussion

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 (BW), GA, and RDS severity were the most frequently assessed factors.

Although in most studies, average BW was lower in infants who failed INSURE, the evidence for BW 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 BW ($< 1,000 \text{ g}$), 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 cutoff value for the ELBW group, which complicates direct comparison of these results. Although based on only 5 studies, being small for GA does not appear to be an independent risk factor of INSURE failure. Thus, although there is some suggestion that an extremely low BW might be associated with an increased risk of INSURE failure, the evidence is weakened by inconsistency and does not allow determining a safe cutoff value or making clear recommendations for clinical practice.

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

Predictive factor	Study	Univariate analysis				Multivariate analysis	
		variable	INSURE SUCCESS group	INSURE FAILURE group	<i>p</i> value	variable	measure of association (95% CI)
Cesarean section	Brix et al. [16], 2014		72/100 (72)	23/33 (70)	N.r.	CS	aOR 1.5 (0.6–4.0)
	Cherif et al. [17], 2008		48/74 (65)	24/35 (68)	NS		
	Danaei et al. [18], 2017		90/113 (80)	66/79 (83)	0.496		
	Dani et al. [19], 2010		47/68 (69)	6/7 (86)	0.630		
	Gharebaghi et al. [20], 2014		65/102 (64)	27/45 (60)	0.66		
	Li et al. [21], 2014		27/42 (64)	25/29 (86)	0.04	CS	aOR 1.89 (0.66–5.43)
	Najafian et al. [23], 2014		25/29 (64)	14/16 (36)	0.995*		
	Naseh and Yekta [24], 2014		154/179 (77)	N.r.	0.032*		
	Ognean et al. [25], 2016		13/31 (42)	15/16 (58)	0.244		
	Tagare et al. [26], 2014		6/16 (38)	7/12 (58)	0.274°		
Antenatal steroids	Brix et al. [16], 2014	Number of patients <i>without</i> ACS (%)	9/100 (9)	4/33 (13)	N.r.	No ACS	aOR 1.4 (0.4–5.4)
	Cherif et al. [17], 2008		40/74 (54)	18/35 (51)	NS		
	Dani et al. [19], 2010		63/68 (93)	5/7 (71)	0.761		
	Gharebaghi et al. [20], 2014		67 (65.7)	33/45 (73)	0.36		
	Li et al. [21], 2014		38/42 (90)	19/29 (66)	0.009		
	Morales-Barquet et al. [22], 2017		22/112 (20)	20/71 (28)	0.062	ACS	aOR 0.49 (0.17–1.45)
	Naseh and Yekta [24], 2014		163/179 (73)	N.r.	0.606*		
	Ognean et al. [25], 2016		16/31 (52)	9/26 (35)	0.204		
	Tagare et al. [26], 2014		9/16 (56)	9/12 (75)	0.306		
Apgar at 1'	Brix et al. [16], 2014	Number of patients with Apgar at 1' <7 (%)	30/100 (30)	8/33 (25)	N.r.	Apgar at 1' <7	aOR 0.5 (0.2–0.3)
	Ognean et al. [25], 2016		5.8±1.8	4.6±2.3	0.047		
	Gharebaghi et al. [20], 2014		7.6±1.3	5.7±2.1	<0.001		
Apgar at 5'	Ancora et al. [14], 2010	Median (range)	8 (6–9)	8 (3–9)	0.341	Apgar at 5' <7	aOR 1.4 (0.2–10.6)
	Azzabi et al. [15], 2016		8.3±1.3	6.9±1.6	0.008		
	Brix et al. [16], 2014	Number of patients with Apgar at 5' <7 (%)	4/100 (4)	2/33 (2)	N.r.		
	Cherif et al. [17], 2008		8.9±1.4	8.7±1.2	NS		
	Dani et al. [19], 2010	Median (range)	8 (1–9)	9 (7–9)	0.514		
	Gharebaghi et al. [20], 2014		8.8±1.0	7.6±1.5	0.007		
	Li et al. [21], 2014		9.4±0.8	9.0±1.3	0.331		
	Morales-Barquet et al. [22], 2017	Median (range)	9 (4–9)	9 (7–9)	0.881		
	Ognean et al. [25], 2016		7.8±1.3	6.3±2.6	0.038		
SGA	Brix et al. [16], 2014		42/100 (42)	12/33 (36)	N.r.	SGA	aOR 0.9 (0.4–2.0)
	Cherif et al. [17], 2008		6/74 (8)	9/35 (26)	0.02	SGA	aOR 6.34 (0.96–55.14)
	Li et al. [21], 2014		10/42 (24)	9/29 (31)	0.499		
	Morales-Barquet et al. [22], 2017		28/112 (25)	24/71 (34)	0.198		
	Ognean et al. [25], 2016		17/31 (55)	12/26 (46)	0.522	SGA	aOR 0.71 (0.25–2.01)

Table 3 (continued)

Predictive factor	Study	Univariate analysis				Multivariate analysis	
		variable	INSURE SUCCESS group	INSURE FAILURE group	<i>p</i> value	variable	measure of association (95% CI)
Hemoglobin	Brix et al. [16], 2014	Number of patients with Hb <8.5 mmol/L (%)	2/100 (3)	5/33 (21)	N.r.	Hb <8.5 mmol/L	aOR 5.1 (1.0–25.8)
	Cherif et al. [17], 2008	Number of patients with Hb <14 g/dL (%)	8/74 (11)	10/35 (28)	0.01	Hb <14 g/L [#]	aOR 8.33 (0.99–40.23)
		Serum Hb level, g/dL	16.3±2.2	15.8±1.7	NS		
Procalcitonin	Talosi et al. [27], 2014	ng/mL	18.9±19.3	45.3±63.0	0.0085		
Complicated pregnancy	Ognean et al. [25], 2016		6/31 (19)	13/26 (50)	0.014	Complicated pregnancy	aOR 4.17 (1.28–13.52)
Pneumothorax	Brix et al. [16], 2014		2/100 (2)	8/33 (25)	<0.05	Pneumothorax	aOR 1.32 (0.5–4.6)
	Cherif et al. [17], 2008		0/74 (0)	2/35 (6)	NS		
	Danaei et al. [18], 2017		3/113 (2)	25/79 (31)	<0.001		
	Dani et al. [19], 2010		0/68 (0)	2/7 (28)	0.001		
	Li et al. [21], 2014		0/42 (0)	1/29 (3)	0.851		
	Najafian et al. [23], 2014		0/29 (0)	2/16 (12)	0.999*		
Infection	Cherif et al. [17], 2008	Early-onset infection	10/74 (13)	5/35 (14)	NS	Sepsis	aOR 1.13 (0.75–1.69)
		Nosocomial sepsis	18/74 (24)	10/35 (28)	NS		
	Danaei et al. [18], 2017	Sepsis	18/113 (16)	20/79 (25)	0.108		
		Chorioamnionitis	3/68 (4)	0/7 (0)	0.656		
	Morales-Barquet et al. [22], 2017	Sepsis	16/68 (24)	5/7 (71)	0.025		
		Sepsis (%)	74/112 (66)	50/71 (70)	0.539		
	Najafian et al. [23], 2014	Chorioamnionitis	7/112 (7)	11/71 (17)	0.062		
		Sepsis	6/29 (21)	4/16 (25)	0.641*		
	Ognean et al. [25], 2016	Chorioamnionitis	1/31 (3)	0/26 (0)	0.544		

* ANOVA (analysis of variance); ° *p* value for normal vaginal delivery; # conversion factor for hemoglobin for mmol/L to g/dL = 1.6114 (8.5 mmol/L = 13.70 g/dL). Values in univariate analyses represent either mean ± SD or number of patients (%), unless otherwise noted. N.r., not reported; CS, caesarean section; aOR, adjusted OR; NS, not significant; ACS, antenatal corticosteroids; SGA, small for gestational age; Hb, hemoglobin. Typography.

In many of the included studies, the average GA 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 GA increases the odds of INSURE failure with a factor 1.8 [16]. Particularly infants with a GA of <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 GA 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 cutoff point. The use of pCO₂ is supported by 2 studies showing that hypercapnia (pCO₂ >50–55 mm Hg) 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 cutoff 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 pO₂ and pCO₂. The paO₂/FiO₂-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 cutoff values that were used in the 2 studies (i.e., <195 and <218) would mean that, for example, an infant with a pO_2 of 70 mm Hg would be at increased risk of failing INSURE if the FiO_2 prior to INSURE exceeds 0.32–0.36, which is only slightly above the level of indication for surfactant therapy.

The remaining RDS severity indices were analyzed using heterogeneous methodologies. Other composite indices, which 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]. Among them are the oxygenation index (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 hemoglobin 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. [16] 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. Lactate has not been investigated in any of the other included studies. Differences in pH before INSURE procedure were addressed in 5 of the included studies, but none of them found a significant association with INSURE failure [14, 16, 17, 20, 27]. The association with low serum hemoglobin 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 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 were 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 randomized controlled trials and meta-analyses suggest that MIST/LISA is superior to INSURE in terms of a composite outcome of death or bronchopulmonary dysplasia [37]. However, despite promising results from randomized controlled trials [37, 38–41], the treatment failure rate of MIST/LISA remains considerable. Results on failure rate are variable, taking into account more recent literature, ranging from 30 [42] 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, GA was the only early factor found to be significantly associated with failure in univariate analysis [43]. This observation was confirmed in a more recent retrospective cohort study, where MIST failure increased with decreasing GA. Other predictive factors for MIST failure were an elevated CRP value, absence of antenatal steroids, and surfactant dose [42]. 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.

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 2 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]. Second, 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 GA and BW, 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 cutoff values per index. As a result, we could not conduct a meta-analysis.

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 BW (< 750–1,000 g), a lower GA, 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.

Implications for Future Research

There is a need for large and 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.

Conclusion

We presented a complete overview of early predictive factors for INSURE failure. Extremely low BW, low GA, 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.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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