Surfactant Administration in Preterm Neonates Using Laryngeal Mask Airway: A Randomized Clinical Trial

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Abstract- In this study, we aimed to compare the efficacy of laryngeal mask airway (LMA) versus endotracheal tube in the early rescue surfactant administration in premature neonates with respiratory distress syndrome (RDS). This randomized, clinical trial evaluated 60 premature neonates with RDS. Numbered envelopes randomly assigned 30 neonates to the intervention group to receive 2.5 ml/kg/dose surfactant (Curosurf) via LMA and 30 to the control group to receive 2.5 ml/kg/dose surfactant via an endotracheal tube using the INSURE technique, exclusively during the first two hours of life. There were no differences in the requirement for mechanical ventilation (23.3% vs. 20%, *P*=0.75), requirement for second dose surfactant (13.3% vs. 6.7%, *P*=0.67), bronchopulmonary dysplasia (13.3% vs. 6.7%, *P*=0.67), pneumothorax (6.7% vs. 0%, *P*=0.49), and intraventricular hemorrhage (10% vs. 10%, *P*=1) between neonates who received surfactant via LMA versus those who received surfactant via endotracheal tube. LMA seems to be an effective and less invasive alternative to endotracheal intubation for surfactant delivery in premature neonates with RDS.

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Introduction

Neonatal respiratory distress syndrome (RDS) is defined as the respiratory failure in premature newborns that is secondary to surfactant deficiency. An estimated 35% of preterm neonates develop RDS, making it a major cause of mortality and morbidity in this population (1,2). Surfactant administration in premature neonates with RDS significantly reduces mortality, morbidity, and chronic lung diseases in these infants (2). Surfactant is traditionally administered via an endotracheal tube (ETT), which is an invasive method and requires expertise clinicians. Furthermore, endotracheal intubation could be complicated by transient airway obstruction, oxygen desaturation, bradycardia, increasing systemic and intracranial pressure, and changes in cerebral blood flow and brain electrical activity (2,3). Considering these possible adverse effects searching for noninvasive or minimally invasive alternative methods for surfactant administration in neonates with RDS seems necessary (2,3).

Laryngeal mask airway (LMA) is a supraglottic device that is routinely used in adults as an effective and minimally invasive alternative to the ETT (3). By the availability of smaller sizes LMA, some efforts were made to use this device for surfactant delivery in premature neonates (4-6). The promising reports on the feasibility of using LMA to deliver surfactant in premature neonates led to the initiation of several randomized controlled trials (RCT) that aimed to compare surfactant administration via LMA to either the routine method of using ETT (7-9), or to no surfactant administration in preterm neonates with RDS (10,11). All these studies concluded that using LMA is feasible and effective and could be used as a less invasive alternative to the ETT for surfactant delivery in preterm neonates with RDS (7-11).

All published studies have evaluated LMA for delayed administration of surfactant (within 72 hours of life) in preterm neonates (7-11), while using LMA for early administration of surfactant (within 2 hours of life)

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which is significantly more effective than late surfactant administration (2), has not been evaluated in the literature (2,12). Further, due to the paucity of the current evidence, using LMA for surfactant delivery in preterm neonates should be limited to clinical trials (12-14), and more RCTs are required to assess the efficacy and possible complications of this method, especially in settings with low resources (8,9,11-14).

We conducted this RCT to compare the efficacy and adverse effects of early surfactant administration through LMA and ETT in preterm neonates with RDS, exclusively within the first two hours of their lives.

Materials and Methods

Study population and design

This prospective, randomized, open-label, controlled, trial was conducted on 60 admitted premature neonates with RDS from December 2014 through December 2015. The neonates were considered eligible if they were born at less than 37 weeks gestation, weighed ≥1200 grams, had a diagnosis of RDS within the first two hours of life, requiring continuous positive airway pressure (CPAP) support ≥5 cm H2O (with or without nasal intermittent positive pressure ventilation (PPV)), plus fraction of inspired oxygen (FiO_2) between 0.30-0.60 to maintain blood oxygen saturation (SpO_2) between 88 to 95%. Exclusion criteria were: having a previous intubation, major malformations (craniofacial, cardiac or thoracic), mean blood pressure < 40 mmHg, Apgar score ≤3 at 5 minutes, requiring FiO_2 concentrations >0.60, pneumothorax prior to enrollment, apnea requiring assisted ventilation, diaphragmatic hernia, and parents' refusal to give informed consent.

After explaining the procedure, informed written consent was obtained from the parents. The neonates were randomly allocated into two groups: the ETT group to receive surfactant via ETT using the INSURE approach (intubation-surfactant administration–extubation), and the LMA group to receive surfactant via LMA (Figure 1).

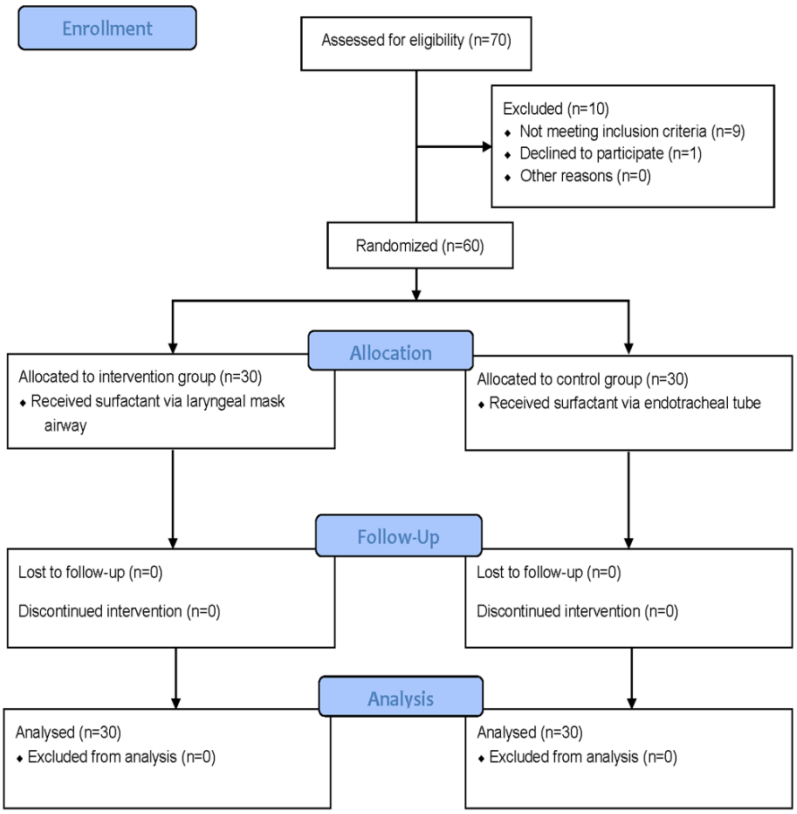

Figure 1. Consort flow chart of the study

Simple randomization with a 1:1 allocation ratio was used in this study. Sequence generation was performed using a computerized random number generator. Allocation concealment was performed through consecutive opaque envelopes that were opened sequentially and only after the participant's name and other details were written on the appropriate envelope.

The primary outcome was the failure of the surfactant treatment strategy to prevent RDS related mechanical ventilation during the admission period. Secondary outcomes were the requirement for a second dose of surfactant, duration of CPAP, length of neonatal intensive care unit (NICU) admission, rate of bronchopulmonary dysplasia (BPD) (dependence on O2 or any ventilatory support at 28 days of age or 36 weeks postmenstrual age), pneumothorax, intraventricular hemorrhage (IVH) and mortality. This study was approved by the institutional review board (IRB) of our institution and is registered at the Iranian Registry of Clinical Trials (www.irct.ir), which is a Primary Registry in the WHO Registry Network (Registration Number: IRCT201602019568N14).

Surfactant administration

In this study, we exclusively evaluated the early administration of surfactant, which is now strongly recommended and has been shown to be more effective than the delayed surfactant treatment (1). Before surfactant administration an orogastric tube was placed for all neonates to decompress the stomach (15). In the randomly assigned ETT group, after administration of a single dose of morphine (0.1 mg/kg) as the recommended premedication (16), we used the INSURE approach (intubation-surfactant administration-rapid extubation) for surfactant delivery. Because CO_2 detectors are not widely available in our country we used the clinical assessments for verifying the correct placement of the endotracheal tube (15). Surfactant (Curosurf ®, Chiesi Pharmaceuticals, Parma, Italy) 2.5 ml/kg per dose was given via endotracheal tube in 2-4 aliquots, with 3-4 adequate PPVs between the aliquots, followed by PPV for at least 5 minutes before reinstituting the prior nasal CPAP, if possible, within 15 minutes of surfactant administration.

In the randomly assigned LMA group, a size 1 Classic LMA (LMA Classic ™, Benelux, Netherland) was inserted according to the American Academy of Pediatrics (AAP) guidelines, and the cuff was inflated with 2ml of air (cuff pressure equal to 20 cm H_2O) (15). Three adequate PPVs were verified by noting adequate chest movements and SpO_2 for at least one minute. Surfactant 2.5 ml/kg per dose was given in 2-4 aliquots to spontaneously breathing infants, at the distal end of the LMA using a shortened 5 French-feeding catheter, with 3-4 adequate PPVs between aliquots, followed by PPV for at least 5 minutes before reinstituting the prior nasal CPAP, if possible, within 15 minutes of surfactant administration.

Surfactant re-dosing

Routine clinical protocols for surfactant administration were carried out in both groups. If the FiO2 was 20% more than the baseline, or if the FiO2 was ≥0.60 or ≥0.30 associated with the worsening of RDS clinical signs (increasing ACORN respiratory distress score) (Table 1) (17), surfactant was re-dosed using the same method of the initial surfactant administration after excluding other causes of respiratory insufficiency (2,17). If the neonates required third and subsequent doses, the surfactant was administered via an endotracheal tube in either group.

Table 1. The Acute Care of At-Risk Newborns (ACORN) respiratory distress score, adapted from Solimano *et al*., The ACORN, Acute Care of at-Risk Newborns. 3rd Ed (15)

	Points		
	0	**1**	**2**
Respiratory rate (per minute)	40-60	60-80	> 80
Oxygen requirement	None	≤ 50%	> 50%
Retractions	None	Mild to moderate	Severe
Grunting	None	With stimulation	Continuous at rest
Breath sounds on auscultation	Easily heard throughout	Decreased	Barely heard
Prematurity (weeks)	> 34	30 - 34	< 30

- Mild respiratory distress: a score < 5
- Moderate respiratory distress: a score of 5 - 8
- Severe respiratory distress: a score > 8

Mechanical ventilation

Treatment failure was defined as the requirement for mechanical ventilation after surfactant administration. Mechanical ventilation was started if any one of the following criteria were met:

1. Developing severe respiratory distress: defined as having a respiratory distress score >8 based on the Acute Care of At Risk Newborns (ACORN) respiratory distress score (Table 1) (17).
2. Developing severe acid-base imbalance: defined as an arterial blood gas (ABG) score >3 based on the ABG scoring system for assisted ventilation (Table 2) (18).
3. Having apnea defined as the cessation of respiration for ≥20 seconds during the first 24 hours of life.

Table 2. Arterial blood gas (ABG) scoring system for assisted ventilation, adapted from Goldsmith, J, and Karotkin, E. Assisted Ventilation of the Neonate, 5th Ed (16)

	Points			
	0	**1**	**2**	**3**
pH	> 7.30	7.20-7.29	7.10-7.19	< 7.10
paO_2 (mmHg)	> 60	50-60	< 50	< 50
$paCO_2$ (mmHg)	< 50	50-60	61-70	> 70

paO_2: partial pressure of oxygen in arterial blood, $paCO_2$: partial pressure of carbon dioxide in arterial blood

Statistical analysis

The sample size was calculated for a power of 80% and α=0.05. Data were displayed using Mean and Standard Deviation (SD), median, and range. Comparisons between two groups were performed using the t-test for independent samples and the Mann-Whitney U test, while the analysis for dichotomous outcomes was performed using the Chi-squared analysis and Fisher's exact test when appropriate. The level of statistical significance was set at $P<0.05$.

Results

This study evaluated 60 premature neonates with RDS who required surfactant therapy during the first two hours of their lives. Thirty neonates were randomly assigned to the LMA group to receive surfactant via LMA, and thirty were randomly assigned to the ETT group to receive surfactant via ETT (Figure 1). The mean±standard deviation (SD) for gestational age was 32.5±2.3 weeks; birth weight was 1910±514 grams. Of the neonates, 31 (51.7%) were male, 29 (48.3%) were female, and 53 (88.3%) had received antenatal steroids. There were no significant differences in the demographics between the two study groups (Table 3).

Table 3. Comparison of the demographics between the two study groups

Demographics	**LMA group n=30**	**ETT group n=30**	***P***
Gestational Age at birth (weeks) (Mean±SD)	32.6 ± 2.3	32.4 ± 2.3	0.70
Birth weight (grams) (Mean ± SD)	1970 ± 520	1850 ± 496	0.49
Male gender [Number (%)]	15 (50%)	16 (53.3%)	0.79
Antenatal steroids [Number (%)]	27 (90%)	26 (86.7%)	0.68

LMA: laryngeal mask airway, ETT: endotracheal tube, n: number, SD: Standard Deviation, N.S: Non-Significant, FiO_2: the fraction of inspired oxygen, C/S: cesarean section

Seven neonates in the LMA group and 6 neonates in the ETT group required mechanical ventilation after surfactant treatment (23.3% vs. 20%, $P=0.75$). Four neonates in the LMA group and 2 neonates in the ETT group required a second dose of surfactant within 12 hours of the first (13.3% vs. 6.7%, $P=0.67$), while no neonate in either group required a third dose of surfactant administration (Table 4). There were no statistically significant differences between the LMA and ETT groups in relation to the occurrence of BPD

(13.3% vs. 6.7%, *P*=0.67), pneumothorax (6.7% vs. 0%, *P*=0.49), and IVH (10% vs. 10%, *P*=1.00) (Table 4). Also, there were no statistically significant differences in the duration of CPAP (*P*=0.70), and length of NICU admission (*P*=0.47) between the neonates in the LMA vs. ETT groups (Table 4).

Table 4. Comparison of the study outcomes the two study groups

Outcomes	LMA group n = 30	ETT group n = 30	*P*
Requirement for mechanical ventilation, [N (%)]	7 (23.3%)	6 (20%)	0.75
Requirement for second dose of surfactant, [N (%)]	4 (13.3%)	2 (6.7%)	0.67
Bronchopulmonary dysplasia, [N (%)]	4 (13.3%)	2 (6.7%)	0.67
Pneumothorax, [N (%)]	2 (6.7%)	0	0.49
Intraventricular Hemorrhage, [N (%)]	3 (10%)	3 (10%)	1
Duration of CPAP (hours), [Median (Range)]	11 (3 – 180)	16.5 (3 - 143)	0.7
Days of NICU admission (days), [Median (Range)]	7 (2 - 34)	8.5 (2 - 39)	0.47

LMA: laryngeal mask airway, ETT: endotracheal tube, n: number, SD: Standard Deviation, CPAP: Continuous positive airway pressure ventilation, NICU: neonatal intensive care unit

Discussion

In this RCT of sixty premature neonates with RDS, early surfactant administration via LMA and ETT were equally effective and reduced the requirement for subsequent mechanical ventilation. Further, we did not observe significant differences in the adverse outcomes by using the two surfactant treatment methods.

In the early 1980s, exogenous surfactant administration via an ETT was used for the first time to treat RDS in preterm infants (19), and since then, this treatment has been considered as a safe and effective therapy for managing the immaturity related surfactant deficiency (2). The widely used INSURE strategy for surfactant administration was introduced by Verder *et al*., in 1992 (20); in this method, the neonate is intubated, surfactant administered via an ETT, and then the neonate is rapidly extubated to nasal CPAP (3,20). Although the INSURE method of surfactant administration is highly effective in decreasing the severity of neonatal RDS and improving pulmonary function, this technique requires trained personnel and remains invasive that could be complicated by transient airway obstruction, oxygen desaturation, increasing systemic and intracranial pressure (2,3). Due to the mentioned limitations of the endotracheal intubation, several less invasive alternative methods have been proposed for surfactant administration and are being investigated in different RCTs (3). LMA was first used for neonatal surfactant administration in two newborns with RDS in 2004 (4), which was followed by several reports of successfully using LMA in human and animal studies (5,6,21), and several RCTs with promising results (7-11).

The current study is the first trial to compare the administration of surfactant via LMA versus ETT exclusively within the first two hours of life in neonates with RDS; both methods effectively decreased supplemental oxygen requirement and resulted in the prevention of mechanical ventilation in more than 75% of cases. Furthermore, there were no statistically significant differences in the adverse outcomes, including BPD, pneumothorax, and IVH between the two groups. Similar results were found in previous studies that evaluated delayed administration of surfactant using LMA within the first 72 hours of life (7-11). Pinheiro *et al*., and Barbosa *et al*., in two different trials compared delayed surfactant administration using LMA versus using ETT in premature neonates with RDS and concluded that surfactant administration through both methods was similarly effective with no differences in the adverse neonatal outcomes between

the two groups (8,9). In another trial Sadeghnia *et al*., compared using i-gel (a supraglottic device similar to LMA with the exception of having a distensible silicone gel combination instead of pneumatically distensible cuff) to ETT for delayed surfactant administration in neonates with RDS and concluded that using i-gel was more successful in improving oxygenation than using ETT by the INSURE method (7). Finally, Attridge *et al*., and Roberts *et al*., in two separate trials compared delayed administration of surfactant via LMA to a control group that only received nasal CPAP and concluded that surfactant administration via LMA significantly decreases the requirement for supplemental oxygen and mechanical ventilation in neonatal RDS (10,11).

Due to the limited evidence on using LMA in very preterm neonates, the AAP recommends using LMA only for term and preterm newborns at≥ 34 weeks, and those who weigh≥ 2000 grams (15). Our study demonstrated that the smallest sized LMA could also be successfully used for preterm neonates who weigh≥ 1200 grams. There are also other studies that used LMA for surfactant delivery in neonates weighing >800 grams (10), ≥1000 grams (9), and ≥1250 grams (11), and all documented that LMA can be successfully used for surfactant delivery in very preterm neonates. Furthermore, there is accumulating evidence in human and animal studies that LMA is easier to use, requires less time and fewer attempts, and also causes less trauma and neurocirculatory disturbances compared to the ETT (21-26). All these results indicate that LMA could be used as an effective and less invasive alternative to the ETT for surfactant delivery in neonates with RDS.

The strengths of our study are its randomized controlled design, and being the first study to evaluate the efficacy of LMA for exclusively early surfactant administration within the first two hours of life in preterm neonates with RDS. Also, this study is among the first trials comparing surfactant administration via LMA and ETT in neonates with respiratory distress syndrome. One main limitation of our study is that the sample size was calculated only to address the main outcome that was the failure of the surfactant treatment strategy to prevent mechanical ventilation, which makes our study underpowered to properly assess other rare but very serious adverse outcomes including IVH, pneumothorax, and mortality. Another limitation is that we did not evaluate the time from decision of administering surfactant to the time of its delivery in our study. These factors should be addressed in future studies since they are important in proper decision making. Furthermore, studies are required to compare total hospital charges and cost-effectiveness between using LMA and endotracheal tube in preterm neonates with RDS.

Early administration of surfactant during the first two hours of life via LMA and ETT seem to be equally effective with no significant differences in the adverse outcomes in premature neonates with RDS. However, more RCTs with larger sample sizes are required to confirm these results and to assess the rare adverse outcomes and compare the cost-effectiveness of using LMA versus ETT for early surfactant administration in neonates with RDS.

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