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Less Invasive Surfactant Administration Comparing Intubation-surfactant-extubation and Endotracheal Catheter in Dakahlia Hospitals

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a primary cause of neonatal respiratory morbidity and mortality. For years, preterm infants with RDS have been managed with a combination of tracheal intubation and surfactant replacement therapy (SRT) followed by mechanical ventilation. SRT in preterm infants has been effective in decreasing infant morbidity and mortality and a major therapy in intubated preterm infants with respiratory distress after birth.

Aim of the Work: To detect the efficiency of less invasive surfactant administration (LISA) and compare endotracheal catheter with intubation-surfactant-extubation (INSURE).

Subjects and methods: Clinical trial. The current study was applied in the Neonatal Intensive Care Unit (NICU) in three hospitals in Dakahlia Governorate: Mit Ghamr General Hospital, Talkha General Hospital and Senbellawein General Hospital during the period from January to June 2019.

Results: The results of this study suggest that thin tracheal catheter is the widely accepted route of surfactant replacement therapy and has slightly better outcome than the INSURE method. Future studies with a large number of patients are needed to show that this manner is as effective as thin tracheal catheter surfactant administration.

Conclusion: The conclusion of the study is that thin tracheal catheter is the widely accepted route of surfactant replacement therapy, and has similar efficacy, feasibility and safety to its administration via endotracheal tube with higher success and less complications.

Keywords: Respiratory distress syndrome, surfactant replacement therapy, preterm infants.

INTRODUCTION

Respiratory distress syndrome in preterm infants is usually treated with surfactant therapy on mechanical ventilation. However, intubation could cause complications and mechanical ventilation could cause acute lung injury. Therefore, continuous positive airway pressure (CPAP) has been introduced instead of mechanical ventilation for spontaneously breathing infants after birth in attempt of decreasing acute lung injury. INSURE technique was the first method to replace mechanical ventilation and has been widely accepted. The procedure has been reported to reduce the need for further intubation and duration of treatment [(1)].

Less invasive surfactant administration (LISA) has been done over the years with several techniques. These LISA techniques include Intra-pharyngeal surfactant instillation, surfactant nebulization, surfactant instillation via a laryngeal mask and surfactant instillation via a thin endotracheal catheter, which is the most common one. Recent reviews updated several LISA methods based on feasibility studies, cohort studies, and clinical trials [(2)].

PATIENTS AND METHODS

The current study was applied in the Neonatal Intensive Care Unit (NICU), in three hospitals in Dakahlia Governorate: Mit Ghamr General Hospital, Talkha General Hospital and Senbellawein General Hospital during the period from January to June 2019.

Target Population:

Included preterm infants under 36 weeks with respiratory distress syndrome, who were admitted to NICU of Mit Ghamr General Hospital, Talkha General Hospital and Senbellawein General Hospital. The studied infants were classified into two groups according to way of surfactant administration:

- Group I: (n=18) using thin catheter (TCA).
- Group II: (n=18) using Intubate-Surfactant-Extubate (Insure).

Ethical approval: Approval was obtained from Institutional Review Board (IRB) in Faculty of Medicine, Zagazig University and approval of the 3 hospitals. Informed consent was obtained from parents of the participants after being informed about the aims and process of the study as well as applicable objectives.

Inclusion criteria:

1- Preterm neonates with gestational age (GA) between 30-36 weeks immediately after birth (first 24 hours of life), their weights were compatible with their GA according to fetal growth charts.
2- Silverman-Anderson (SA) score greater than four and/or respiratory frequency > 60/m and/or

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fraction of inspired oxygen (FiO2) ≥ 0.40 to maintain oxygen saturation (SpO2) 91-95%.

3- Clinical diagnosis of RDS including cyanosis, grunting, nasal flaring, poor feeding and tachypnea (more than 60 breaths per minute). There may also be retractions in the intercostal, subcostal or suprasternal spaces. These typical distress symptoms occur in premature infant immediately after birth.
4- Typical RDS chest X-ray.

Exclusion criteria: Infant above 36 weeks, infants with weights incompatible with their GA, infant with congenital anomalies, infant with congenital heart disease, infant of addicted mothers and infants with history of risk factors for sepsis and maternal disease (cardiac, hypertensive, diabetic, anemic).

Data collection

- Demographic data including name, age, gender, residence of baby and data of diseases of mother and type and time of delivery. In addition, estimation of gestational ages according to both history and examination using New Ballard Score.
- History of resuscitation in the delivery room.
- Clinical examination including general examination for vital signs and other systems including apneic spells, need for supplemented oxygen, need for ventilation and grade of respiratory distress.
- Laboratory investigations were done for all patients including for diagnosis of RDS (Arterial blood gases (ABG)).
  For sepsis exclusion: Complete blood count (CBC). C-reactive protein (CRP)
- Radiological investigations were done for all patients including chest X-ray before and 6 hours after surfactant therapy
- Evaluation of the respiratory distress grade using Downs RDS scoring [3]: Grade I (mild): tachypnea, working ala nasi and tachycardia. Grade II (moderate): chest retraction "in-drawing" (e.g. subcostal and intercostal) due to moderate hypoxia. Grade III (severe): grunting, which is due to severe hypoxia and indicate alveolar lesion. Grade IV: cyanosis and disturbed consciousness and endotracheal tube is needed here.

Methods:

The cases had been selected from the NICU in Mit Ghamr General Hospital, Talkha General Hospital and Senbellawein General Hospital.

- Attending neonatologists-identified eligible patients according to the inclusion and exclusion criteria after clinical evaluation, chest X-ray, arterial blood gas analysis, and assignment of surfactant treatment.

Procedures

- Prenatal, perinatal, and postnatal patient conditions and laboratory findings, vital signs, Silverman-Anderson (SA) score and arterial blood gas analysis was registered before the procedures.
- All patients received the same surfactant preparation (poractant- , 120 mg/1.5 mL) and the same dose (200 mg/kg), by bolus instillation within the first 8 h of age. The chest X-ray findings were evaluated before and six hours after surfactant.

Outcome of the Procedures

The primary outcome was a reduction in patient's FiO2 requirement following surfactant administration and the need to repeat the surfactant dose.

The secondary outcome was to decrease mortality and complications of mechanical ventilation such as pneumothorax, BPD and retinopathy of prematurity (ROP).

Follow up

- Chest x-ray was obtained from all infants before and 6 hours after surfactant therapy and RDS severity was determined by an expert pediatric radiologist.
- Arterial blood gas parameters were recorded at admission and 6 hours after surfactant administration.
- Clinical severity of RDS had been assessed using Downs RDS scoring system in all patients.
- Variables such as RDS score, oxygen demand before and after the administration of surfactant, need for re-intubation or frequent use of the surfactant, radiological evidence of recovery of RDS and other complications during hospitalization were measured. For all patients, checklists had been completed by a NICU nurse who was unaware of the aim of the study and patients' groups.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.

- P-value >0.05 was considered insignificant.

RESULTS

No statistically significant difference was detected between the studied groups regarding gestational age, sex and weight (Table 1).

The respiratory rate changes and grunting in infants of group I was significantly improved after treatment. While there were no significant changes in other clinical findings after treatment (Table 2).

The respiratory rate changes and chest retraction in infants of group II was significantly improved after treatment. While there were no significant changes in other clinical findings after treatment (Table 3).

The respiratory rate changes of infants of group I recorded statistically significant improvement than those of group II. While other clinical findings of infants of both groups after treatment were almost the same with no statistically significant difference among them (Table 4).

Both groups were matched as regards heart rate and blood pressure that were assessed after treatment, with no statistical significant difference between them (Table 5).

Both groups were matched concerning levels of ABG that were measured after treatment with no statistically significant difference between them (Table 6).

72.2% of infants of group II improved on CPAP versus 83.3% of group I, while only 5.6% of group I died versus 11.1% of group II with no statistically significant difference among both of them (Table 7).

Table (1): Demographic data of the studied population

Variables	Frequency				x^2 \ t-test*	P-value
	Group I (n=18)		Group II (n=18)			
Sex	**N**	**%**	**N**	**%**		
Male	**12**	**66.7**	**11**	**61.1**	0.12	0.729 NS
Female	**6**	**33.3**	**7**	**38.9**		
Gestational age	**32.3 ± 2.19**		**32.6 ± 1.57**		0.545*	0.601 NS
Weight \kg	**1.7 ± 0.47**		**1.9 ± 0.52**		**0.973***	**0.331 NS**

Table (2): Difference in clinical findings of RDS in group I before and after treatment

Clinical Picture	Group I (n=18)		Paired-t/X^2	p
Symptoms & Signs	**Before**	**After**		
Respiratory rate / min (mean ± SD)	68 ± 2.2 /min	61 ± 2.6 /min	3.9	**0.046 S**
Grunting	11 cases (61.1%)	3 cases (16.1%)7	2.1	**0.049 S**
Chest retraction	13 cases (78%)	9 cases (50%)	2.9	0.087 NS
Cyanosis	0 cases (0%)	0 cases (0%)	-----	----------
Nasal flaring	5 cases (27.7%)	2 cases (11.1%)	1.6	0.203 NS

Table (3): Difference in clinical findings of RDS in group II before and after treatment

	Group II (n=18)		Paired-t/X^2	
Symptoms & Signs	**Before**	**After**		**P**
Respiratory rate / min (mean ± SD)	67 ± 3.2 /min	62 ± 3.4 /min	4.5	**0.048 S**
Grunting	6 cases (33.3%)	2 cases (11.1%)	2.5	0.113 NS
Chest retraction	13 cases (72%)	6 cases (33.3%)	5.3	**0.021 S**
Cyanosis	0 cases (0%)	0 cases (0%)	-----	----------
Nasal flaring	7 cases (38%)	3 cases (16.1%)	2.1	0.238 NS

Table (4): Difference in arterial blood gases measured before and after treatment among group I

Variables	Group I		t-test	P-value
	Before	After		
PH Mean ± SD	**7.32 ± 0.03**	**7.36 ± 0.04**	**4.73**	**<0.001 HS**
Co2 Mean ± SD	**45.6 ± 11.7**	**44.7 ± 11.81**	0.416	0.681 NS
Hco3 Mean ± SD	**20.8 ± 3.21**	**21.2 ± 3.4**	**0.514**	**0.614 NS**

Table (5): Clinical data assessed after treatment among the studied population

Variables	Mean ± SD		t-test	P-value
	Group I=18	Group II=18		
HR (b/min)	**130.4 ± 14.04**	**128.5 ± 18.6**	0.357	0.726 NS
Systolic BP (mmHg)	**60.8 ± 10.8**	**62.6 ± 7.85**	0.547	0.588 NS
Diastolic BP (mmHg)	**39.5 ± 6.34**	**39.3 ± 4.72**	**0.09**	**0.929 NS**

Table (6): Arterial blood gases measured after treatment among the studied population

Variables	Mean ± SD		t-test	P-value
	Group I=18	Group II=18		
PH (units)	**7.36 ± 0.04**	**7.33 ± 0.08**	1.07	0.293 NS
Co2 (units)	**44.7 ± 11.8**	**47.6 ± 13.61**	0.678	0.501 NS
Hco3 (units)	**21.2 ± 3.4**	**22.5 ± 3.7**	**1.1**	**0.281 NS**

Table (7): Outcome among the studied population

X –ray	Frequency				x^2	P-value
	Group I=18		Group II=18			
	N	%	N	%		
CPAP	**15**	**83.3**	**13**	**72.2**	0.676	0.713 NS
Ventilation	**2**	**11.1**	**3**	**16.7**		
Died	**1**	**5.6**	**2**	**11.1**		

DISCUSSION

In this study, thirty-six preterm infants suffering from respiratory distress syndrome less than 36 weeks of gestation were immediately admitted to the Neonatal Intensive Care Unit (NICU) during the period from January until June 2019. The studied infants were classified into two groups according to way of surfactant administration. Thus, the current study aimed to detect efficiency of less invasive surfactant administration (LISA), and compare it with Intubate-Surfactant-Extubate (INSURE) method.

The study showed no statistically significant difference between both studied groups regarding demographic data such as gestational age, gender and birth weight. These results are in agreement with **Jaba *et al.*** [4]. Also, **Waal *et al.*** [5] run with our study as they conducted a prospective observational cohort study on infants treated with surfactant via the MIST procedure. They demonstrated that mean birth weight was 1,230 ± 391, mean gestational age was 29.3 ± 2.1 and 55% were male infants. In the present study, regarding the clinical findings of RDS, respiratory rate showed mild statistically significant improvement after treatment in both groups. Our statistics also showed that respiratory rate was significantly improved after treatment in group I more than group II **(p < 0.001)**. As for grunting, only group I showed statistically significant improvement after treatment **(p < 0.049)** while group II showed improvement but with no statistical significance. On the other hand, chest retraction showed statistically significant improvement in group II **(p < 21)** while in group I showed improvement but with no statistical significance. Regarding nasal flaring, results were almost the same and showed no statistically significant difference between the two groups while there was an improvement of the clinical findings in each group after treatment than before. The most common clinical finding reported was chest retraction while neither of the two groups reported cyanosis before or after (Tables 2, 3 and 4).

Waal *et al.* [5] verified that tachypnea and respiratory effort showed a significant, rapid, and

persistent decrease following LISA more than Insure while other clinical findings did not change in the first hour after treatment.

We found that the fluctuation of heart rate, blood pressure and arterial blood gases before and after treatment were almost matched in both groups as they all were within normal ranges and all infants in the study showed good vital signs. While there was change within the same group in ABG,

Same results as ours were obtained by **Jaba *et al.*** [4], who reported a significant improvement in pH over time after intervention, which may be conducted to reduction in the need for supplemental oxygen and decrease of Co_2 with increase of HCo_3. **Lau** [6] results match ours regarding the radiological and laboratory data. In addition, **Mirnia *et al.*** [7] found that Hco_3 increased 2 h after surfactant administration in TCA group that was statistically significant **($p < 0.05$)**. PH increased in both groups 2 h after surfactant administration but there was no difference statistically.

In contrary, **Mirnia *et al.*** [8] reported that there were no significant differences between the 2 groups regarding ABG and radiological examination. This is because their RDS cases were grades and their clinical examinations were relatively good before treatment.

Regarding pneumothorax, our results is similar to **Lau *et al.*** [6] who observed that the incidence of pneumothorax was reported in 290 infants (147 infants with thin catheter and 143 infants with INSURE), while was fewer in the thin catheter group compared to the INSURE group (7.5% vs 9.1%). While, ours was (11.1% vs 22.2%). In addition, they are similar to our results regarding the need for supplemental oxygen as they showed a significant reduction in the need for oxygen with the use of thin catheter **($P < .001$)** compared to INSURE.

Another study illustrated similar results to ours on the need of supplemental oxygen. **Berneau *et al.*** [9] found that Infants who received the LISA procedure had a lower duration of mechanical ventilation and a lower incidence of supplemental oxygen requirments.

As for broncho-pulmonary dysplasia, **Kanmaz *et al.*** [10] contradict our results as they found a lower incidence of broncho-pulmonary dysplasia in the MIST group than the INSURE group (10% versus 20%) while our results showed that it was slightly more in the TCA group than INSURE (16.6% verses 5.5%). This may be due to lower incidence of this complication and some of those infants in our study had patent ductus arteriosus (PDA), which increases the incidence of broncho-pulmonary dysplasia. **Kribs *et al.*** [11] conducted a study comparing TCA method with surfactant by intubation and mechanichal ventilation (rathar than InSurE method). They reported absolute reduction of all complications including broncho-pulmonary dysplasia and pneumothorax in the TCA group compared to mechanical ventilation and reduction of days of oxygen consumption.

According to days of hospital stay, **Heidarzadeh *et al.*** [12] compared between MIST (n=38) vs. INSURE (n=42) and reached the same conclusion as we did that the MIST group required shorter duration of CPAP and hospital stay than the INSURE group.

In the present study, the outcome between both groups showed comparable results regarding improvement on CPAP (83.3% vs 72.2%, in group I and II, respectively), need for mechanical ventilation (MV) (11.1% vs 16.7%, in group I and II, respectively), and infants who died (5.6% vs 11.1%, in group I and II, respectively). Similar results regarding the previous data were obtained by **Kribs *et al.*** [13]. Regarding improvement on CPAP and need for MV, three trials compared TCA to InSurE and had the same results as we did as they showed a decrease in the need for mechanical ventilation in the first 72 h of life (typical RR 0.72, 95% CI 0.53–0.97; typical RD –0.09, 95% CI –0.18 to –0.01) [8].

Regarding mortality rate, six trials agree with our results **Mirnia *et al.*** [8] as they all demonstrated no difference in mortality with TCA. **Jaba *et al.*** [4] also confirmed our results when they reported statistically non-significant difference between the two groups regarding need for mechanical ventilation or occurrence of death during hospital stay (both were lower among thin tracheal catheter group but non-significant). **Mohammadizadeh *et al.*** [14] come in consistence with that there was no significant difference between groups regarding to need for mechanical ventilation during the first 72 h of birth and there was no difference in deaths rate between the two groups. **Lau *et al.*** [6] observed that data on the number of infants requiring mechanical ventilation within the first 72 hours in both the LISA thin catheter and INSURE groups were fewer in the thin catheter group compared to the INSURE group. The meta-analysis revealed a 32.3% reduction in the need for mechanical ventilation within the first 72 hours with thin catheter compared to INSURE. Our results confirmed the results of **Mirnia *et al.*** [8] study which included Infants 27–32 weeks' gestational age stabilized on CPAP and reported that mortality was lower in the TCA group with no difference in mechanical ventilation in the first 72 h. **Kanmaz *et al.*** [10] 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%) but showed no difference in rate of deaths. **Bao *et al.*** [15] compared between MIST (n=47) vs. INSURE (n=43), and reported that No differences in rate of MV in the first 72 hours, duration of oxygen and neonatal morbidities. Duration of MV and CPAP significantly less in the MIST group.

Olivier *et al.* [16], in randomized controlled trial in 12 NICUs in Canada, concluded that

administration of surfactant by a 5-Fr feeding tube compared to administration by an endotracheal tube after intubation and mechanical ventilation was associated with a significant reduction in the need for mechanical ventilation. In addition, they did not report death or broncho-pulmonary dysplasia in any of their infant. **Kribs *et al.* [(11)]** concluded that TCA group was less frequently mechanically ventilated in the first 72 h of life. **Aguar *et al.* [(17)]** findings were a bit different with ours as they reported that 74% of the infants in the INSURE group did not need MV in comparison with 66% of in the MIST group. Also **Krajewski *et al.* [(18)]** do not agree with our results and reported that MV reduced within 72 h, 3.9% in insure group vs. 11.7% in the LISA group.

However, it is difficult to make comparisons between the different studies due to differences in the gestational ages of the studied infants, birth weight, and number of infants involved [(17)] as well as difference in patient demographics [(15)]. In addition, factors such as early application of mechanical ventilation, which increases the risk of complications of this intervention, could explain the significant differences in above mentioned short-.and long-term outcomes between different studies [(14)].

CONCLUSION AND RECOMMENDATIONS

The study concluded that thin tracheal catheter is the widely accepted route of surfactant replacement therapy, and has similar efficacy, feasibility and safety to its administration via endotracheal tube with higher success and less complications. Further studies are needed to resolve uncertainties of the thin tracheal catheter method, including appropriate infant selection, optimal surfactant dosage and administration method and need for sedation.

DECLARATION

- No Funds
- All participants in the research agreed to publish.

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