NORMAL SALINE NEBULIZATION IN PREVENTING EXTUBATION FAILURE IN NEONATES, A RANDOMIZED CONTROL TRIAL

By

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ABSTRACT

Background: *Recurrent extubation and reintubation leads to higher morbidity and can cause long-term disabilities in neonatal population. Failure of extubation may result from several factors including alveolar atelectasis, and inadequate pulmonary mechanics. Normal saline is effective and widely used inhaled therapeutic agents either alone or in combination with other agents.*

Aim of the work: *To evaluate the effect of normal saline nebulization in prevention of reintubation in neonates admitted to Neonatal Intensive Care Units (NICUs) of Ain Shams University Hospitals over 6 months period (from 8/2021 till 2/2022).*

Subjects and Methods: *Sixty freshly extubated neonates were randomly allocated equally into 2 groups (intervention group and control group). Intervention group receives 4 mL of 0.9% saline nebulization was given every 4 hours for maximum of 72 hours. Patients were followed clinically till discharge and using lung ultrasound. Primary outcome was reintubation within 72 hours.*

Results: *No significant differences between both groups in demographic data ($p > 0.05$). There was no significant difference in reintubation incidence ($p=0.222$), duration of respiratory support till discharge ($p= 0.438$) or final outcome ($p=0.718$) between the two groups. Length of NICU stay and need for post extubation noninvasive ventilation were significantly longer in saline group ($p <0.038$ & $p<0.008$ respectively). Lung ultrasound scores of case group were significantly higher at enrollment and 72 hours later ($p<0.01$) however, this didn't influence incidence of reintubation or final outcome ($p = 0.812$ & $p=0.7$ respectively). Worse LUS scores significantly correlated with both longer hospital stay and duration of respiratory support ($p<0.05$).*

Conclusion: *Our data doesn't support using saline nebulization post extubation. Using lung ultrasound might be of value in guiding clinical decisions and predicting outcomes from neonatal respiratory diseases.*

Key words: *LUSS, POCUS, nebulized saline, NICU.*

INTRODUCTION

Since its introduction in the sixties, mechanical ventilation has become a lifesaving practice that has improved the outcome of neonates with respiratory failure. However, it is not without complications. Early weaning from invasive ventilation is mandatory to decrease neonatal morbidities **(Eltomey et al., 2019)**.

Timing of extubation and determining when the patient can return to the physiological respiration is crucial as it is constantly accompanied by some risk of failure and need for reintubation **(Bilan et al., 2009)**. Failure of extubation may result from several factors including alveolar atelectasis, subglottic edema, or inadequate pulmonary mechanics **(Abdel-Rahim et al., 2020)**.

Recurrent attempts of extubation and reintubation lead to higher morbidity and can cause long-term respiratory or neurologic disabilities **(Gollu et al., 2016)**.

Respiratory kinesiotherapy as nebulization techniques improves ventilation and facilitates the elimination of secretions to avoid bronchial obstruction, allowing good maintenance of airways, and facilitating ventilator weaning **(Rocha et al., 2018)**.

Nebulized normal saline has historically been used as a placebo typically in studies examining bronchodilator medications and sputum expectorants or used as a carrier to medications. Nowadays, the use of nebulized, normal (0.9% isotonic) saline -as a method of enhancing mucociliary clearance- has become a clinically accepted adjunct to physiotherapy in the treatment of many chronic lung conditions **(House et al., 2020)**.

Lung ultrasonography is a powerful diagnostic technique and a non-invasive research tool used to describe several neonatal respiratory disorders in a qualitative manner. It is not only useful in predicting failure of non-invasive ventilation and the need for invasive ventilation, but also has a great value in anticipating extubation success with higher diagnostic accuracy and sensitivity compared to chest x-ray **(Kurepa et al., 2018)**. In general, patients with lower lung ultrasound scores show a better chance of extubation success **(Soummer et al., 2012)**.

AIM OF THE WORK

To evaluate the effect of normal saline nebulization in prevention of reintubation in neonates admitted to Neonatal Intensive Care Units (NICUs) of Ain Shams University Hospitals over 6 months period (from 8/2021 till 2/2022).

PATIENTS AND METHODS

Patients:

All intubated neonates were eligible for enrolment. Once extubated, only babies who had a respiratory disease as a primary and only cause of intubation were included. Babies with upper obstructive airway disease, those who have neurological, cardiac, surgical, or metabolic comorbidity that might interfere with extubation were excluded.

Randomization:

Post extubation, 60 enrolled neonates were allocated (by simple randomization) into one of 2 groups (intervention group and control group) in ratio 1:1; a study group received standard care + normal saline nebulization for at least 72 hours while control group received standard care only.

Standard care:

As per unit protocol at extubation, neonates are extubated either to air or noninvasive modes of ventilation. Clinicians decide the mode of respiratory support required based on the baby’s clinical picture work of breathing, blood gas and saturation. This support includes non-invasive modes of respiratory support (Continuous positive air way pressure CPAP, non-invasive positive pressure ventilation NIPPV mode, nasal high frequency, high flow oxygen, low flow oxygen, or incubator oxygen). Chest X rays are ordered post extubation on demand (e.g., if oxygen requirements increase, suspected air leak, poor respiratory effort, suspected post-extubation lung collapse or increased work of breathing). Neonates can receive chest physiotherapy, positioning and nasal care as required.

Study intervention:

Once extubated, neonates in the study group receive 4 mL of 0.9% saline nebulization was given every 4 hours for maximum of 72 hours **(Manrique et al., 2020)**. Nebulization was discontinued earlier if the baby was reintubated within 72 hours post-extubation (study end point).

Saline nebulization was delivered by jet nebulizer with face mask. It uses compressed oxygen passing through a narrow orifice at 6–9 L/min **(Ibrahim et al., 2015)**. Nebulization was received while patient was kept in supine, semi sitting position as tolerated, before receiving feeds.

Methods:

All babies were subject to thorough examination and detailed history taking including gestational age, birth weight, mode of delivery, maternal history of chronic illness, or history suggestive of infection.

Data collected during NICU stay included circumstances of intubation (e.g., presenting respiratory symptoms, main cause of intubation) and ventilation (e.g., mode of ventilation, ventilation settings, duration of invasive ventilation, total duration of any assisted ventilation).

Extubation data included decision to extubate (planned or accidental), status of respiratory support 72 hours after extubation, reintubation at any point and the reason for that.

Lung ultrasonography (LUS):

LUS was performed by a single dedicated operator using US Scanner Samsung (HM70A) and probe (LA-16AD) to calculate the score at enrolment and post extubation by 72 hours.

LUS technique and interpretation:

During the LUS, Infants were placed in a position that is suitable for the examination to make sure that the exam did not interfere with infant's clinical management. Generally, the infant is placed in supine position.

Each lung was divided into 3 areas (upper anterior, lower anterior, and lateral) and examined using a linear microprobe through both transverse and longitudinal scans. For each lung area, a 0- to 3-point score was given (total score ranging from 0-18). 0=Normal aeration, 1=multiple well-defined B lines (> 2 lines) 2= multiple coalescent B lines (B2), 3=presence of a tissue pattern characterized by dynamic air bronchograms **(Soummer et al., 2012)**.

Study outcomes:

The primary outcome was reintubation within 72 hours post-extubation. The secondary outcome was LUS score 72 hours post-extubation compared to LUS at enrollment.

Sample size justification:

Sample size was calculated using PASS 11.0 and based on a study carried out by **Zhang et al.,**

2011. Group Sample size of 30 in group 1 and 30 in group 2 achieve 90% power to detect a difference of -1.4 between the null hypothesis that both group means are 6.0 and the alternative hypothesis that the mean of group 2 is 7.4 with estimated group standard deviations of 1.2 and 1.5 and with a significance level (alpha) of 0.01000 using a two-sided, two sample t-test. Sample size inflated by 10% to account for attrition problem in prospective studies.

Ethical consideration:

1. An informed consent was obtained from parents or the legal guardians before enrollment in the study.
2. An approval by the local ethical committee of Ain Shams University was obtained before the study was conducted.
3. The patients have the right to withdraw from the study at any time.
4. The authors declare no potential conflicts of interest with respect to the research authorship and\or publications of this article.
5. All data of the patients and results of the study are confidential, and patients have the right to keep it.
6. Authors received no financial support for research, authorship and\or publications of this article.

Statistical Analysis:

Package for Social Science (IBM SPSS) version 23 was used. The quantitative data were presented as mean, standard deviations and ranges for parametric variables and median, inter-quartile range (IQR) for non-parametric variables. Qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was done by using Chi-square test. The comparison between two groups with quantitative data and parametric distribution was done by using Independent t-test. While the comparison between two groups with quantitative data and non-parametric distribution was done by using Mann-Whitney test. The comparison between two paired groups with quantitative data and non-parametric distribution was done by using Willcoxon test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Receiver operating characteristic curve (ROC) was used in the quantitative form to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Area under curve (AUC) for the studied parameters to differentiate between patients without nebulizer and patients with nebulizer.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Nonsignificant, P < 0.05: Significant, P < 0.01: Highly significant.

RESULTS

Table (1): Demographic data of study groups

		Patients without nebulizer (control)	Patients with nebulizer (cases)	P-value
		No. = 30(%)	No. = 30(%)	
Gender	**Male**	11 (36.7)	15 (50.0)	0.297
Gestational age (weeks)	**Mean ± SD**	34.67 ± 2.93	34.33 ± 2.31	0.626
	Range	28 – 40	29 – 37	
Weight (Kg)	**Mean ± SD**	2.15 ± 0.66	2.23 ± 0.67	0.631
	Range	1 – 3.3	0.9 – 3.6	
APGAR 1st min	**Median (IQR)**	6 (4 – 7)	6 (5 – 7)	0.213
	Range	2 – 8	2 – 8	
APGAR 5th min	**Median (IQR)**	8 (7 – 9)	9 (8 – 9)	0.254
	Range	6 – 9	7 – 9	

SD; standard deviation, IQR; Interquartile range. APGAR; Appearance, Pulse, Grimace, Activity, and Respiration. Data expressed as mean +SD where T -test was applied for comparison or as median and IQR where Mann Whitney test was used or as number (%) where Chi-square test(x2) was applied for comparison

Table (1) shows no significant differences between both groups in demographic data of the studied neonates (p-values > 0.05).

Table (2): Intubation circumstances:

		Patients without nebulizer(control)	Patients with nebulizer(cases)	P-value
		No. = 30	No. = 30	
Age of intubation	Median (IQR)	1(1-2)	1(1-3)	0.052
	Range	1-14	1-20	
Signs of respiratory distress	Hypoxia	14 (46.7%)	10 (33.3%)	0.292
	WOB	21 (70.0%)	25 (83.3%)	0.222
	Hypercapnia	4 (13.3%)	1 (3.3%)	0.161
Underlying respiratory illness	RDS	11 (36.7%)	16 (53.3%)	0.194
	TTN	7 (23.3%)	5(16.7 %)	0.519
	PPHTN	6 (20.0 %)	3(10.0%)	0.292
	Pneumonia	8 (26.7 %)	8 (26.7 %)	1.000

RDS; respiratory distress syndrome, TTN; transient tachypnea of newborn, PPHTN; Persistent pulmonary hypertension, WOB; work of breathing. Data expressed as median and IQR where Mann Whitney test was used or as number (%) where Chi-square test(x2) was applied for comparison

Table 2 shows that the median age of intubation was 1 day in all study population. Increased work of breathing was the main respiratory sign leading to intubation (70 % of control group vs 83.3 % in case group). RDS was the most common underlying respiratory illness in both study groups, yet there was no significant difference between the two groups in the previously mentioned 3 parameters.

Table (3): Post extubation respiratory status:

		Patients without nebulizer (control)	Patients with nebulizer(cases)	P-value
		No. (%)	No. (%)	
Need for post extubation noninvasive ventilation		26 (86.7)	30 (100.0)	**0.038**
Duration of post extubation NIV till discharge	Median (IQR)	3 (2 – 5)	3 (2 – 8)	0.438
	Range	1 – 20	1 – 20	

NIV: noninvasive ventilation. Data expressed as median and IQR where Mann Whitney test was used or as number (%) where Chi-square test(x2) was applied for comparison.

Table 3 shows that 100% of patients in case group needed post extubation NIV compared to 86.7 % in control group (p-value <0.05). No statistical difference was found between the two study groups in duration of NIV used post extubation (p= 0.438).

Table (4): Patients' outcomes and length of NICU stay:

		Patients without nebulizer(control) No. = 30	Patients with nebulizer(cases) No. = 30	P-value
Reintubation within 72 hours		5 (16.7%)	9 (30.0%)	0.222
Length of stay (days)	Median (IQR)	15 (7 – 22)	21 (16 – 27)	**0.002**
	Range	4 – 25	7 – 55	
Final outcome	Discharge	26 (86.7%)	25 (83.3%)	0.718
	Died	4 (13.3%)	5 (16.7%)	

Data expressed as median and IQR where Mann Whitney test was used or as number (%) where Chi-square test(x2) was applied for comparison

Table 4 shows that the days spent in NICU were significantly higher in case group than control with ($p < 0.01$) yet there was no difference in final outcome. There was Also no significant difference in reintubation incidence between the two groups ($p > 0.05$).

Table (5): Comparison between LUS scores in both groups at enrollment and 72 hours later in both groups:

		Patients without nebulizer (control) No. = 30	Patients with nebulizer(cases) No. = 30	P-value
LUS score at enrollment	**Median (IQR)**	5 (4 - 7)	9 (6 - 10)	**0.000**
	Range	1 – 9	3 – 12	
LUS score after 72 hours	**Median (IQR)**	4 (3 - 5)	6 (3 - 8)	**0.032**
	Range	1 – 8	1 – 11	
Difference	**Median (IQR)**	2 (3 - 1)	3 (5 - 1)	0.181
	Range	6 – 4	8 – 3	
Wilcoxon Rank test		**3.300**	**2.708**	
P-value		**0.001**	**0.007**	

LUS; lung ultrasound. Data expressed as median and IQR where Mann Whitney test was used and the comparison between two paired groups with quantitative data and non-parametric distribution was done by using Willcoxon test

Table 5 shows that the lung ultrasound scores of case group were significantly higher both at enrollment and 72 hours later ($p = 0.000$ & $p < 0.032$ respectively). Within the same group, LUS scores improved significantly at 72 hours compared to at enrollment score. No significant difference was encountered between the degree of improvement in both groups (p-value >0.05).

Table (6): The relation between the LUS at enrollment and incidence of reintubation:

		Reintubation within 72 hours		P-value
		No	Yes	
LUS score at enrollment	Median (IQR)	7 (5 – 9)	7 (5 – 9)	0.812
	Range	3 – 12	1 – 11	

LUS; lung ultrasound. Data expressed as median and IQR where Mann Whitney test was used.

Table (6) shows that the reintubation incidence was independent from the LUS at enrollment in both study groups (p-value = 0.812).

Table (7): Correlation between the length of NICU stay and duration on NIV post extubation with the lung ultrasound results:

	Length of NICU stay in days		Non-invasive duration of ventilator support	
	r*	p-value	r*	p-value
LUS score at enrollment	0.259	**0.045**	0.288	**0.026**
LUS score after 72 hrs	0.451	0.002	0.275	0.075

LUS: lung ultrasound. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. *Spearman's rank coefficient of correlation.

Table 7 shows that LUS score at enrollment correlated significantly with duration of post extubation NIV till discharge (p-value <0.05). The worse the LUS, the longer the ventilatory support duration and the longer NICU stay.

Table (8): Correlation between the LUS scores and patient's outcome

		Discharge	Died	P-value
		No. = 51	No. = 9	
LUS score at enrollment	Median (IQR)	7 (5 - 9)	6 (4 - 9)	0.707
	Range	1 – 12	2 – 10	
LUS score after 72 hrs	Median (IQR)	4 (3 - 6)	5.5 (3 - 8)	0.770
	Range	1 – 11	3 – 8	

LUS: Lung ultrasound. Data expressed as median and IQR where Mann Whitney test was used.

Table 8 shows that the final outcome of patients in both study groups was not correlated with the LUS scores (p-value > 0.05).

DISCUSSION

The current study aimed to evaluate the effect of normal saline nebulization in prevention of reintubation and causing respiratory improvement evidenced by decreasing patients' LUS scores.

In the current study, most neonates were intubated because of RDS as an underlying pathology, with increased work of breathing as the most common sign of respiratory distress.

Similarly, **Clark, 2005** examined 1011 neonates with gestational age of ≥ 34 weeks and found that RDS was the most common respiratory disease in babies who needed intubation in the first 72 hours of life. Also, **Saisamorn et al., (2022)** concluded that increased work of breathing was the most common respiratory sign in babies intubated in the delivery room after applying 5 respiratory indices (upper chest movement, lower chest retractions, xiphoid retractions, dilatation of the nares, and expiratory grunt).

In the current RCT, 100% of neonates in case group were extubated to noninvasive respiratory support compared to 86% in control group. However, the total duration on NIV till discharge did not show any significant difference.

Noninvasive ventilation is currently a popular mode to support the newly extubated neonates. **Mayordomo-Colunga et al., (2010)** found that post extubation NIV was useful in avoiding reintubation in high-risk children when applied immediately after extubation. In addition, **Maccari et al., (2014)** concluded in their study that applying aerosol while on NIV could be more effective than using aerosol alone. Their finding was proven by augmented radio aerosol in the study group.

As per our primary outcome, incidence of reintubation was comparable between the two groups (p-value =0.2).

Similarly, **Shein et al., (2016)** discussed the effect of nebulized hypertonic saline versus normal saline inhalation on mechanically ventilated and freshly extubated children till 7 days post extubation. They concluded that there was no significant difference between both agents regarding hospital stay or reintubation rate (p-value >0.99).

On the contrary, **Xyu et al., (2021)** in their study on prevention of bronchopulmonary dysplasia reported higher rate of reintubation (p-value <0.05) in the group of normal saline inhalation compared to budesonide inhalation.

In the current RCT, length of NICU stay was significantly prolonged in case group compared to control group. However, no difference was found in the final outcome between the two groups.

Similarly in a historical study on preterm infants who required long NICU stay, with average NICU stay of 125 days (+/- 102 days), Davison et al (1994) summed up that there was no correlation with survival at discharge.

Moreover, and regarding the relation between saline inhalation and length of stay, **Badget et al., (2015)** in a metanalysis of 11 trials concluded that inhaled saline significantly improved the symptoms and decreased the need of hospitalization among outpatient infants with acute bronchiolitis aged from 2 to less than 24 months while among hospitalized infants, it reduced the length of stay but the evidence was of low quality due to the heterogeneity of length of stay.

Moreover, **Pukai et al., (2020)** conducted a study on children less than 2 years suffering from moderate acute bronchiolitis or pneumonia to determine the effect of nebulized normal saline. They found significant improvement in respiratory distress symptoms and oxygen saturation between 0 to 4 hours of starting treatment with significant decrease in need for hospitalization.

In our study, LUS was used to assess respiratory status at time of extubation and 72 hours later. LUS scores (collectively and on each side) were higher in case group compared to control group. Overall, poorer LUS scores were correlated with longer hospital stay and longer total duration of respiratory support. However, they were not correlated with final outcome. This might indicate the benefit of LUS in predicting different neonatal outcomes.

On the same line, in their 5 years study, **Elsayed et al., (2022)** concluded from their study over five years on point-of-care LUS that not only was LUS beneficial in diagnosing neonatal respiratory diseases, but also it influenced the clinical management.

Additionally, **Di Mauro et al., (2020)** proved in their study on 111 infants that lung ultrasound could correlate with the clinical progression by assessing the lung status in infants with acute bronchiolitis aged less than 2 months (p-value <0.001).

Furthermore, **Bobillo-perez et al., (2021)** also concluded that

LUS score showed a strong correlation with the length of hospital stay in infants with bronchiolitis needing pediatric intensive care unit admission.

As per the patients' outcomes, and similar to our results, **Stecher et al., (2021)** reported that lung ultrasound score has good predictive value for duration of mechanical ventilation but not on the final outcome (p = 0.02).

On the other hand, **Raimondi et al., (2019)** studied 65 neonates with a gestational age of 34–40 weeks with transient tachypnea of newborn and found that LUS score correlated well with the clinical course (p-value 0.02).

In the current study, there was no significant relation between LUS scores and incidence of reintubation within 72 hours in our study groups with median LUS scores at enrollment of 7.

On the contrary, **Eltomey et al., (2019)** found that lower LUS scores were found in patients with successful extubation (mean 4 ± 2.42, median 5) compared to patients who failed extubation (mean 9 ± 1.92, median 9).

Moreover, **Soliman et al., (2021)** in their study on 66 preterm infants ≤ 34 weeks with RDS concluded that LUS could predict extubation success at a cutoff point 11 with high sensitivity but low specificity of 91% and 69%. Additionally, **Liang et al., (2021)** studied the role of LUS score in extubation failure in neonates with RDS. They estimated a cutoff point of 9 to anticipate extubation failure with p-value <0.001. **Elsayed et al., (2022)** classified RDS based on LUS score into mild (score 0-9) and moderate to severe (score 10-18). Since the median of LUS scores in both groups was 7, this might indicate that the LUS can well correlate with extubation failure in poorer lung conditions (higher scores than 9). However, this need further studies to be proved.

STUDY LIMITATIONS

The paucity of data regarding the use of saline nebulization in neonatal population in general, in post extubation in particular made it extremely difficult to compare our results to literature and have a better understating to the outcomes. However, we did our best to interpret the results in view of the current available data.

CONCLUSION

Our data doesn't support using saline nebulization post extubation. Using lung ultrasound might be of value in guiding clinical decisions and predicting outcomes from neonatal respiratory diseases.

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