Diagnostic utility of lung ultrasound in predicting the need for surfactant therapy in preterm neonates with respiratory distress

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Abstract

Objectives: Primary objective was to determine the diagnostic accuracy of lung ultrasound score (LUS) in predicting the need for surfactant therapy in preterm neonates (<34 weeks) with respiratory distress. Secondary objectives were to correlate LUS with corresponding oxygen saturation to fraction of inspired oxygen ratio (SpO₂/FiO₂), arterial/Alveolar oxygen pressure ratio (a/A) and chest x-ray (CXR) findings. Working hypothesis: LUS reflects lung aeration and will correlate with requirement of surfactant in preterm neonates with respiratory distress. It can be an accurate and timely predictor for surfactant therapy.

Study design: Prospective observational study carried out at a tertiary level NICU in Western India in 2022 enrolling 100 neonates <34 weeks gestation with respiratory distress. Methodology: After initial stabilization of the neonate, LUS was performed and baseline parameters noted. Surfactant was administered as per 2019 European guidelines and LUS was repeated after 6 hours. Results: The mean gestation of enrolled neonates was 31.06 +/- 2.12 weeks and the mean birthweight was 1412 +/- 391 g. Out of 100 neonates, 40 required surfactant therapy. The cutoff LUS for surfactant therapy was 7 (area under curve [AUC] 0.977; 95% CI, 0.947-1; P < 0.001; with sensitivity 93.33%, specificity 92.5%, PPV 94.92%, NPV 90.24%) and the cutoff LUS for second dose of surfactant was 10 (AUC 0.964; 95% CI, 0.913-1; P < 0.001. The score decreased by an average 3.24 (2.44 - 4.05) after 6 hours of first dose and correlated significantly with SpO₂/FiO₂ ratio (-0.750), a/A ratio (-0.650) and CXR findings (0.801). Conclusion: LUS [?] 7 can be considered an accurate marker for surfactant replacement therapy.

Introduction

Being one of the most important causes of morbidity and mortality in preterm neonates, respiratory distress occurs in almost 5.8% of all live births and accounts for 30-40% admissions to neonatal units. The management is based on earlier and timely administration of surfactant along with continuous positive airway pressure (CPAP) support, thereby, avoiding mechanical ventilation. However, the challenge remains to identify the narrow window for administering surfactant.

In the recent times, lung ultrasound has gained a crucial role in early diagnosis and evaluation of respiratory distress in neonates. It is a quick and safe bedside technique and can be repeated several times a day.

Over the years, studies have developed a lung ultrasound score (LUS) for evaluation of lung aeration and prediction of surfactant administration. The same was validated in 2015, demonstrating its utility in the management of respiratory distress syndrome (RDS).

In the previous studies conducted, lung ultrasound aided in guiding early rescue therapy within 2 hours of delivery and thereby reducing the need for repeat dose of surfactant, need for invasive ventilation and
number of days on ventilator. Moreover, when compared with chest x-ray (CXR) scores, it was found to have higher specificity and sensitivity in predicting the need for surfactant replacement therapy in RDS.

Presently, the guidelines for surfactant therapy are based on the requirement of fraction of inspired oxygen (FiO2), the values of which are arbitrary and behind time. The indication of surfactant administration is variable among different neonatal intensive care units (NICU) and is guided by parameters such as CXR grading, arterial/AIveolar oxygen pressure ratio (a/A) and FiO2. Although the utility of LUS in predicting the severity of disease and need for surfactant administration has been reported, data related to lung ultrasound scoring and its accuracy in predicting need for surfactant therapy in preterm neonates with respiratory distress is lacking in the Indian population. It has the potential to be an accurate and early predictor for the need for surfactant therapy in this population cohort, thus, allowing timely treatment and as low as reasonably achievable (ALARA) radiation exposure.

Therefore, this study was conducted to determine the diagnostic accuracy of the lung ultrasound scoring system in predicting the need for surfactant treatment in preterm neonates with respiratory distress and correlate it with corresponding oxygen saturation to fraction of inspired oxygen ratio (SpO2/FiO2), a/A ratio and findings on CXR.

Materials and methods
A single centre prospective observational study was designed and conducted in a tertiary level NICU attached to a medical college. The study was approved by the institutional ethics committee and registered in the clinical trials registry of India (CTRI/2022/07/044166). All neonates <34 weeks gestational age admitted to the NICU within 24 hours of life with respiratory distress were included in the study. An informed consent for the same was obtained from their parents. Neonates with a complex cyanotic congenital heart disease, congenital malformation, chromosomal abnormality, inborn error of metabolism, congenital lung disorder and early onset septic shock were excluded. All the neonates meeting the inclusion criteria were started on non-invasive respiratory support immediately from the time of admission to NICU with an appropriately sized nasal interface. Peak end expiratory pressure (PEEP) was set at 6 cm H2O and FiO2 levels were adjusted to maintain target oxygen saturations within the 90% to 95% target range. In case of failure of CPAP support, mode of respiratory support was stepped up to nasal intermittent positive pressure ventilation (NIPPV) support. Following criteria were used for considering mechanical ventilation (a) repeated episodes of apnea defined as > 4 episodes of apnea per hour or > 2 episodes requiring bag and mask ventilation, (b) hypoxia defined as FiO2 >0.40 to maintain SpO2 between 90-95%, (c) respiratory acidosis with PaCO2 > 60 mmHg and pH < 7.20.

On admission, as per the unit protocol, a baseline arterial blood gas and CXR were done. Baseline lung ultrasound scoring was done denoted as “pre-surf LUS”. The surfactant was administered as per the European consensus guidelines. Following this, a repeat LUS was done after 6 hours of the first dose of surfactant denoted as “post-surf LUS”. A second dose of surfactant at 100 mg/kg of phospholipid was administered if the FiO2 value remained above the cutoff. Apart from this, SpO2/FiO2 ratio and a/A ratio were calculated for all the babies and CXR grading was done based on the radiological characteristics namely radiolucency, cardiac silhouette and air-bronchograms.

Lung ultrasound scoring
Lung ultrasound was done on Philips Affinity 50G machine with the “hockey stick” L15-17 MHz transducer. Each lung was divided into three areas (upper anterior, lower anterior and lateral) and scored.

Each area of the lung was given a score between 0 to 3, the total score ranging from 0 to 18, where 0 indicates A-pattern [(defined by presence of A lines only (horizontal, parallel echogenic lines under the pleural line)]; 1, B-Pattern [defined as the presence of 3 well-spaced B lines (well defined vertical lines that originate on the pleural line, run perpendicular to and obscure the A-lines)]; 2, severe B pattern (defined as the presence of crowded and coalescent B lines with or without consolidation limited to subpleural space and/or white out of lung); 3, extended consolidation (Figure 1).
Lung ultrasound was done by a clinician who had received formal training under senior faculty with at least 6 months of experience in the NICU.

Maternal characteristics (antenatal corticosteroid cover, mode of delivery, risk factors) and neonatal characteristics (gender, gestational age, birth weight, weight for gestational age, requirement of resuscitation at birth, age at enrolment, doses of surfactant, SpO2/FiO2 and a/A ratios just prior to surfactant administration, CXR grading before each dose of surfactant, days on mechanical ventilation, days on non-invasive ventilation, duration of oxygen support (days), length of NICU stay (days), bronchopulmonary dysplasia (%)) were recorded.

Statistics

Categorical variables were expressed as frequency (percentage) and compared using the chi-squared test or Fisher’s exact test, as needed. Quantitative data was expressed as mean-SD. A value of \( p < 0.05 \) was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the LUS to predict the need for surfactant treatment and re-treatment; AUC (area under curve) and reliability data was reported with confidence intervals (CIs). Paired analysis was done for comparison of LUS at 0 and 6 hours post surfactant. Correlational analysis using Pearson’s coefficient was carried out for determining correlation of LUS with SpO2/FiO2 ratio, a/A ratio and CXR grading. To determine the correlation between LUS and CXR at less than 3 and more than three hours of life at enrolment, correlational analysis was carried out using Spearman coefficient.

Sample size was calculated using observational data of the last one year where surfactant was administered to approximately 50% of NICU admitted infants who fulfilled the same inclusion criteria and followed the same surfactant administration protocol. To achieve an AUC of \( > 0.7 \) in ROC analysis with \( \alpha \) error of 0.05 and power of 0.95, 100 samples were needed.

Results

Out of the 100 enrolled neonates, 40 received surfactant therapy. Among these, 18 received beractant and 22 received poractant alfa surfactant preparation. Baseline characteristics of the population are reported in Table 1. The mean gestation of enrolled neonates was 31.06 ± 2.12 weeks and the mean birthweight was 1412 ± 391 g. The median (IQR) age of the neonate at the time of pre-Surf LUS was 1 (1-1) hour. Six neonates among the enrolled expired and fourteen left against medical advice due to financial constraint or futility of treatment in view of poor prognosis. A total of 80 neonates were followed up till discharge. For these, the median (IQR) duration of invasive ventilation was 0.5 (0-2) days, on non-invasive respiratory support was 3 (2-8) days and on oxygen support was 4 days (2-9.5). Four neonates developed broncho-pulmonary dysplasia and their average LUS was 10.75 ± 2.62. Median (IQR) duration of hospital stay of those followed up until discharge was 30.5 days (18.5-40.5). The pre-surf LUS was done at hour of enrolment and with an AUC 0.977, 95% CI (confidence interval) (0.947-1) and \( P < 0.001 \), the cut off score as per ROC curve was 7 (sensitivity 93.33%, specificity 92.5%, positive predictive value 94.92%, negative predictive value 90.24%), Figure 2a. The pre-surf LUS cut off determining requirement of more than one dose of surfactant was 10 (sensitivity 100%, specificity 86.36%, positive predictive value 95.24%, negative predictive value 100%) as per ROC with an AUC 0.964, 95% CI (0.913-1) and \( P < 0.001 \), Figure 2b. In the neonates requiring one dose of surfactant therapy, the LUS decreased by an average 3.24 (2.44-4.05) over 6 hours. The mean difference between pre and post-surf LUS for neonates who received beractant was 3.73 ± 1.35 (P 0.1) and for neonates who received poractant alfa was 2.94 ± 1.76 (P 0.12). Figure 3 shows the distribution of LUS values with the corresponding required FiO2. A correlation of -0.75 (P <0.001) was found between pre-surf LUS and SpO2/FiO2 ratio and of -0.235 (P 0.144) between post-surf LUS and SpO2/FiO2 ratio after 6 hours of surfactant. Between pre-surf LUS and a/A, the correlation was -0.65 (P <0.001) and between post-surf LUS and a/A at 6 hours post therapy, it was -0.075 (P 0.645). Significant correlation was found between pre-surf LUS and first CXR 0.801 (P <0.001) and post-surf LUS and CXR in babies requiring a repeat dose of surfactant 0.811 (P <0.001). The correlation between pre-surf LUS and CXR at <3 hour of enrolment was 0.829 (P <0.001) and >=3 hours of enrolment was 0.832 (P <0.001).
Discussion

In this study, we have found a quantitative lung ultrasound score to be an excellent predictor for the need of surfactant therapy in respiratory distress in preterm neonates. We also noted that this ultrasonographic marker of lung aeration has significant correlation with other clinical markers (a/A ratio, SpO2/FiO2 ratio) and radiological markers (CXR grading) of lung aeration.

In 2012, Raimondi et al. concluded the role of lung ultrasonography in respiratory distress in newborns and since then there have been multiple studies to evaluate the same. It is now increasingly being recognised as a primary modality of choice for assessment of respiratory distress in newborns. However, the existing cutoffs for surfactant replacement therapy have been developed through studies from high income countries and limited data from Indian population exists for the same.

Our study population was similar in terms of gestational age and birth-weight to the studies previously reported. The median time for first LUS assessment in the present study was 1 hour. Taking into account that the study population included newborns that were delivered in the hospital as well as those that were referred from outside hospitals for respiratory distress, this time of assessment was fairly lower as compared to other studies. Perri et al. in their studies reported that the time of first assessment was 3.3 ± 1.8 hours and 2.5 hours. It has been observed that LUS may vary and even worsen in the first four hours of life owing to the airway liquid clearance. Therefore, earlier evaluation within the first 1-2 hours of life is expected to increase the clinical value of the score and reduce false positive results. Previously, the superiority of LUS done as early as 5-10 minutes of life has been reported.

For an objective assessment of requirement of surfactant in neonates with respiratory distress, Brat et al. had developed and established a lung ultrasound score through their study in 2015. However, the LUS cut off as per their study in 65 infants <34 weeks gestation was 4 in comparison to our cut-off score of 7. The LUS cutoff for second dose of surfactant as per our study was 10. Our findings were similar to the study by De Martino et al. who although studied more preterm population (≤30 weeks gestation) but their ultrasound protocol matched ours. In similar studies, Perri et al reported the LUS cutoff for surfactant treatment to be 5 and retreatment 7. The recent study by Raimondi et al including 240 infants calculated 9 as the LUS cutoff for surfactant therapy. Another recently published study from India reported a cutoff score of 9 as optimal for giving surfactant. However, the sensitivity and specificity for the same was lower. Additionally, posterior chest areas were also included in their scoring system to calculate the final LUS. This may account for the differences in their findings.

In the present study, we found a decrease in LUS after surfactant administration. This is expected owing to changes in lung mechanics after surfactant replacement which has previously been reflected upon by other studies. It was also observed that the mean decrease in LUS was higher for beractant as compared to poractant alfa when administered at a dose of 100 mg/kg. This finding however, was not statistically significant.

In this study, the LUS correlated significantly with SpO2/FiO2 ratio, a/A ratio and CXR. Brat et al in their study also showed significant correlation between LUS and a/A ratio and in the studies by Perri et al, significant correlation between LUS and SpO2/FiO2 ratio and LUS and CXR was observed. Raschetti et al in their quality improvement project noted FiO2 to be a later predictor of surfactant therapy as compared to LUS and was shown to have increased the duration of oxygen exposure due to delayed therapy. This affirms that LUS in conjunction with other baseline parameters is a better predictor for surfactant therapy in preterm infants as compared to FiO2 alone.

The strengths of our study include study methodology as per the existing standard guidelines for surfactant use. The first LUS assessment was done relatively earlier as compared to the data from other studies, therefore, the reliability of data is expected to be more when comparing with other baseline parameters at enrolment with a lower false positive rate. The scoring of all lung ultrasounds by a single trained observer eliminated the risk of inter-observer bias.
The study has certain limitations. It was conducted at a single centre and had a relatively smaller sample size. The number of extremely preterm neonates was rather limited therefore limiting the generalizability of the results for that population.

Conclusion

Our study determined the diagnostic accuracy of using a lung ultrasound scoring system in preterm neonates with respiratory distress. It predicted the need of surfactant replacement therapy in neonates with LUS cutoff of 7. The LUS cutoff for requirement of more than one dose of surfactant was 10. The score revealed significant correlation with SpO2/FiO2 and a/A ratios and findings on CXR. However, larger multi centric trials are required to validate these cut offs for surfactant replacement. This study has not explored the role of LUS in infants > 34 weeks gestational age with respiratory distress and this is an area which should be studied further in the Indian setting.

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Conflict of interests

The authors declare no conflict of interest.

Author contributions

Pari Singh: Data collection; data analysis; writing original draft. Suprabha Patnaik: conceptualization; methodology; review and editing; supervision. Arjun Verma: methodology; data collection; review and editing. Reema Garegrat: methodology; data collection; review and editing. Rajesh Maheshwari: conceptualization; review and editing. Pradeep Suryawanshi: conceptualization; review and editing; supervision. All authors read and approved the final manuscript.

References


Figure legends

Figure 1 Score values correspond to different patterns as shown. Scores were given as follows: (A) 0, presence of only A-lines; (B) 1, presence of [?] 3 well-spaced B lines; (C) 2, presence of crowded and coalescent B lines with or without consolidations limited to sub-pleural space; (D) 3, presence of extended consolidation

Figure 2 (A) Receiver Operating Characteristic (ROC) curve for Pre surfactant LUS cut-off for requirement of surfactant therapy (B) Receiver Operating Characteristic (ROC) curve for pre surfactant LUS cut-off for requirement of repeat surfactant therapy

Figure 3 Scatter plot showing distribution of pre-surfactant LUS with corresponding FiO2
A

AUC = 0.977 (95% CI = 0.947-1)

B

AUC = 0.964 (95% CI = 0.913-1)
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