Original Article

The role of lung ultrasound in preterm neonates with respiratory distress in neonatal intensive care unit

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ABSTRACT

Introduction: Up to 29% of late preterm babies suffer from respiratory distress due to which they need to be admitted to neonatal intensive care unit (NICU). Point-of-care ultrasound is a useful tool in critical neonate care, providing valuable information without any risk of ionizing radiation to the newborn. **Materials and Method:** This mono-centric, descriptive, and prospective study was conducted in NICU. Preterm newborns of less than 36 weeks with respiratory distress at birth on non-invasive ventilation were recruited. A lung ultrasound was performed at first 12 h of life and followed till their discharge. Main outcomes need for surfactant treatment. **Results:** Sixty preterm infants (median gestational age: 29 weeks) were recruited. Newborn in the surfactant group requiring ultrasound and intervention was significantly higher than in no surfactant group ($p<0.0001$). In 15 newborns who received surfactant, the first dose was administered at a median age of 4.5 h. In 13 of these 15 newborns, the lung ultrasound scan was subsequently repeated an average of 2 h (Standard deviation or SD: 2) On average, the second dose of surfactant was administered at 24 h of life (SD: 9). **Conclusion:** Early lung ultrasound in preterm infants with respiratory distress appears to be a useful tool with no adverse effects for the patient. It allows a better assessment of respiratory distress by detecting patients with a greater risk of requiring surfactant or mechanical ventilation, even before oxygenation criteria.

Key words: Preterm neonates, Respiratory distress, Lung ultrasound, Surfactant treatment

Preterm neonates with respiratory distress commonly get admitted to neonatal intensive care unit (NICU) [1]. Managing these babies requires precise skills with less invasive techniques, monitoring and treatment. Point-of-care ultrasound (POC-US) is a useful tool in critical neonate care, providing valuable information without any risk of ionizing radiation to the newborns. It is a quick and less expensive. It can be repeated several times and possesses a short learning curve and high inter-observer agreement [2,3]. In the past several years, lung ultrasound has become one of the most exciting applications in the field of the neonatal POC-US. Several recent articles have reported ultrasound imaging to be an equal, if not a more effective diagnostic modality than X-ray.

There is a need to develop creatively engaging strategies that would allow physicians to adapt and accept the use of lung ultrasound in neonates for faster clinical outcome. Lung ultrasound algorithms or protocols, described in the adult population, covers vast amount of validated, and reproducible data and knowledge [4]. On the other hand, no such algorithm exists for the neonatal population known to have relatively specific lung pathology. The goal is to help neonatologists embrace the daily use of the ultrasound as a diagnostic modality.

The semiology currently applied to lung ultrasound in newborns, is similar to that which has been used for many years in adult patients [5]. It is based on interpreting artefacts; findings depend on the proportion of air and fluid in the lungs [6]. A newborn's lungs, even in cases of normal transition after birth, have specific characteristics due to the progressive elimination of fluid that occupies them during the fetal period [7]. The current consensus on the ultrasound pattern describes transient tachypnoea of the newborn (TTN) as a fine pleural line and an absence of consolidations presenting varying degrees of pulmonary oedema (B-lines), while the double lung point sign is not essential [3,8-11]. The ultrasound image described in respiratory distress syndrome (RDS) consists of interstitial syndrome up to white lung (grouped B-lines), variably sized consolidations and an air bronchogram together with a pathological pleural line [9,12,13].

Lung scans in neonatal RDS exhibit a largely homogenous picture, especially during the 1st h of life, as demonstrated by Reimondi *et al*. [3] and in animal immature lung models [14]. However, clinical observations show that in the subsequent days

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of life, pulmonary pathologies in premature neonates often tend to locate in the posterior lung fields [15-17]. This is consistent with the gravitational effect, on lowest parts of the lungs in the supine position. In non-homogeneous lung disorders, the involvement of posterior lung fields seems even more significant. Examples include meconium aspiration syndrome [18] or neonatal ARDS [19]. Posterior scans, therefore, provide a valuable information that should not be overlooked.

The main objective of this study is to correlate the early ultrasound with the need for endotracheal surfactant administration in the first 24 h of life in preterm infants.

METHODS

This was a mono-centric, descriptive, and prospective study conducted in NICU of Hi-Tech Medical and Hospital in Bhubaneswar from January 1, 2020, to January 31, 2021. The study center is an Academic, Tertiary Referral 24- Bed NICU with approximately 250 admissions per year. The hospital manages every kind of neonatal pathology including cardiac surgery. We included preterm infants under the gestational age (GA) of 36 weeks with RDS, defined by the need for respiratory support through continuous positive airway pressure through non-invasive airway distension due to a peripheral oxygen saturation (SpO2)<90% or clinical signs of distress such as polypnea, nasal flutter, and work of breathing. The exclusion criteria were a lack of informed consent, meconium-stained amniotic fluid, infants with congenital malformations or chromosomal abnormalities, and mechanical ventilation or endotracheal surfactant before the ultrasound.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee (Hi-Tech Medical College and Hospital, Bhubaneswar) and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Ultrasound Examinations

The most common high-frequency (≥10 MHz) linear transducer was used. Lung preset is set on the ultrasound machine. Lung ultrasound was performed on a neonate in the radiant warmer. The transducer is oriented in a sagittal plane. Bilateral lungs are examined in the supine and lateral positions. In addition, prone position was commonly used. Each side was divided into three areas: Anterior area between sternum and anterior axillary line, lateral area between anterior and posterior axillary line, and posterior area between the posterior axillary line and the spine [20]. Current neonatal lung literature describes the normal and abnormal lung ultrasound imaging based on the several principles described by Lichteinstein and Mauriat [21]. There are few reports that summarize neonatal findings, encourage lung ultrasound use, and offer further research insights [20,22,23].

Apart from diagnosing specific lung diseases, ultrasound has shown a great promise in the functional monitoring of lung processes and predicting the development of complications [24,25] as follows:

- Lung Sliding: Movement of the parietal against the visceral pleura during respiration is called "lung sliding" [26]. This dynamic phenomenon appears as a shimmering line and it is indicative of a healthy lung. In the M-mode, image appears as a linear pattern in the tissues superficial to the pleural line (sea) and a grainy or "sandy" appearance deeper to the pleural line (shore) creating the "seashore sign" [27].
- A-Lines: These are the horizontal, hyper-echoic, equidistant lines distal to the pleural line. It is a reverberation artifact due to the ultrasound waves being repetitively reflected between the pleura and the transducer [21]. A-line pattern together with lung sliding assures the absence of lung pathology in the scanned area of the lung.
- B-Lines: These are the vertical, hyper-echoic lines extending from pleura distally to the far field without fading. They erase A-lines and move synchronously with the lung sliding. The origin of this phenomenon is accumulation of the lung fluid that widens interlobular septae. Increased presence of the fluid may be due to pneumonia, pulmonary oedema, and transient tachypnea of the newborn (TTN). It may be normal in newborns in the first 48 h, or longer in premature infants, until the lung fluid completely resorbs. Depending on the pathology, B-lines may be unilateral (pneumonia) or bilateral (pulmonary edema, TTN) [28].
- Lung Consolidation: The origin of this pattern is any process that leaves the alveoli without air or filled with fluid. Most common causes are atelectasis, pneumonia, and severe pulmonary oedema. Ultrasound appearance of the consolidated lung gives tissue-like density, called the "heparinization of the lung."

The team in-charge of the patient was blinded to the ultrasound results and the patients were managed according to the usual protocols of the unit. In preterm newborn < 33 weeks, nasal continuous positive airway pressure (nCPAP) was started in the delivery room as part of stabilization. Above this GA, nCPAP was initiated if signs of RDS developed. Infants were supported with nCPAP (5–7 cm H_2O) while breathing spontaneously. We used short bi-nasal prongs or a nasal mask if there was nasal injury as interphases. Surfactant was administered if FiO2>50% to maintain SpO_2 at 90–95% after 1 h of noninvasive support. Intubation criteria were FiO2>60% despite surfactant administration, episodes of apnea (>4/h or >1 requiring positive-pressure ventilation) or respiratory acidosis (pCO_2> 65 mmHg and pH<7.20 in arterial samples). In stable situations (systemic arterial pressure>10^{th} percentile with preserved respiratory effort), synchronized nasal ventilation was applied as a rescue treatment, reserving intubation for cases of persistent intubation criteria. X-rays were performed according to the criteria of the staff in-charge and usually after surfactant administration. If the patient was treated with endotracheal surfactant, an ultrasound scan was repeated within the next 2 h. Clinical data were recorded (including calculation of the oxygen saturation/fraction of inspired oxygen or S/F ratio), as were the patients' medical histories and their progression till discharge. X-ray data were also recorded if they were performed within a maximum of 2 h from the lung ultrasound.

Statistical Analysis

Qualitative variables of interest are expressed as percentages and frequencies, normally distributed continuous variables as means±SD and non-normally distributed variables as medians according to the Kolmogorov–Smirnov test. Pearson's Chi-squared test, Fisher's exact test (two-tailed), Student's t-test, and the Mann–Whitney U-test were used, as needed, to establish baseline differences between the infants in the surfactant and non-surfactant groups. Based on the available literature, sample size was calculated (α error=0.05; 90% power for a bilateral test). First, the whole population was analyzed, then the two subgroups, formed in function of surfactant administration. Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the lung ultrasound in predicting the need for surfactant treatment. Area under the curve (AUC) and reliability data were reported with 95% confidence intervals (CIs). The analyses were performed with SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) and $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 135 newborn infants (GA<36 weeks) were admitted to our NICU. Out of these, 73 were not included for various reasons. 30 (22.2%) did not require respiratory support; 21 (15.5%) were intubated or received surfactant before the ultrasound; 14 (10.3%) were transferred more than 6 h after birth; and 8 (5.9%) died in the early hours of life or had congenital malformations.

Out of the 62 newborns, who met the inclusion criteria, a total of 60 were incorporated in the study. Of these, 40 newborns did not require surfactant, 15 received 1 dose of surfactant (25%) and 5 of them received two doses.

The demographic and clinical characteristics of the groups, classified according to whether or not surfactant was administered were evaluated. Significant differences were found between the groups with respect to GA, sex, Apgar score, need for positive pressure ventilation in the delivery room and certain other clinical variables, such as FiO_2 and S/F ratio (Table 1).

In 15 newborns who received surfactant, the first dose was administered at a median age of 4.5 h (2–14). The patients achieved a median maximum FiO2 of 38% (30–43) when the first dose was administered and 75% had a reduced need for oxygen after the treatment (considering a response to treatment as reduction of at least 20% of the previous FiO2).

The first lung ultrasound was performed at a median of 2.5 h (1.5–4.8) of life and the procedure lasted a median of 5 min (3–8). Eleven chest X-rays (separation≤2 h between lung ultrasound and X-rays) were taken: In four patients from the non-surfactant group and seven from the surfactant group (post-surfactant administration). Therefore, we were unable to draw any conclusions due to this heterogeneity.

The ROC curve yielded an AUC of 0.97 (95% CI 0.92–1, $p<0.00001$). After correcting for GA and prenatal treatment with corticosteroids, the ultrasound scan correlated with the need for surfactant therapy with an adjusted odds ratio (OR) of 3.17 (95% CI, 1.36–7.35).

In 13 out of 15 patients who received one dose of surfactant, the lung ultrasound scan was subsequently repeated at an average of 2±2 h later. In this group, 94% continued to receive respiratory support after 72 h of life. On average, the second dose of surfactant was administered at 24±9 h of life, with a FiO2 of 49±14%.

In patients who finally did require surfactant, their FiO_2 was 34% median (30–44). The graph obtained by drawing the ROC curve for both the ultrasound score and FiO2 (mean: 2.5 h of life) parameters for the overall population, with an AUC of 0.97 (95% CI, 0.93–1) for the ultrasound score and 0.89 (95% CI, 0.77–1) for FiO_2.

Five of the 15 patients who received surfactant required invasive mechanical ventilation in the first 72 h of life (8.3% of the sample).

Table 1: Baseline characteristics of the study population

Baseline characteristics	Surfactant (n=15)	No surfactant (n=45)
GA in weeks [median (range)]	30 (29–32)	33 (31–34)
Female Sex [Value (percentage)]	5 (30)	28 (62)
Birth Weight in gms [Value]	1204	1488
Antenatal Corticosteroids [Value (percentage)]	14 (93.3)	41 (91.1)
Instrumental Delivery/Cesarean Section [Value (percentage)]	13 (86.6)	38 (84.4)
Apgar at 1 minute [median (range)]	6 (6-8)	8 (7-9)
Apgar at 5minute [median (range)]	8 (7-9)	9 (8-9)
Resuscitation required at birth [Value (percentage)]	11 (73.3)	26 (57.7)
Umbilical Artery pH [mean±SD]	7.32±0.2	7.30±0.1

Table 2: Comparison of variables between the groups in terms of surfactant

Variables	Surfactant (n=15) Mean±SD/ Median (range)	No Surfactant (n=45) Mean±SD/Median (range)
Temperature (°C)	36.2±0.6	36.1±0.7
SAP/MAP/DAP (mm-Hg)	45±9/32±8/23±8	44±7/31±6/25±7
Silverman score	5±2	2 (2)
Preductal SpO_2%	92±3	98 (2)
FiO_2%	34 (30-40)	21 (21-29)
pH	7.20±0.04	7.27±0.8
pCO2 (mm-Hg)	63±7	52±11

SAP: Systemic arterial pressure, MAP: Mean arterial pressure, DAP: Diastolic arterial pressure, SpO2: Oxygen saturation, FiO2: Fraction of inspired oxygen, pCO2: Partial pressure of carbon dioxide

DISCUSSION

Our study included a homogeneous sample of preterm infants with a GA of between 29 and 36 weeks and a similar situation at birth with moderate RDS that required noninvasive support (Table 2). Any preterm infants requiring surfactant or intubation in the delivery room were excluded, that justifies the late administration of surfactant (median 4.5 h) and GA, as younger babies are more likely to require stabilization through intubation at birth. Most of the patients received prenatal care, including administration of corticosteroids, and were hemodynamically stable, as reflected by their high Apgar scores, cord blood gas analysis, and the absence of advanced cardiopulmonary resuscitation.

There was a notably low percentage of invasive mechanical ventilation in the first 3 days (<8%), in line with current RDS management recommandations [29]. Several studies have shown that the use of lung ultrasound as part of a global assessment of preterm infants with RDS, provides greater detail than conventional approach, particularly with regard to the differential diagnosis between severe TTN and RDS [30,31]. This is supported by the recent international guidelines for the neonate and the experts who perform lung ultrasound for more accurate assessments [29]. The results of a protocol that includes lung ultrasound as part of the algorithm for endotracheal surfactant administration were also published recently [32].

The previous publications compared the ultrasound pattern with the probability of noninvasive ventilation failure using either qualitative or semi-quantitative measures. The results are summarized in a recent systematic review, which reported an overall sensitivity of 88% (95% CI, 80%–93%), a specificity of 82% (95% CI, 74%–89%), and an OR of 38.58 (95% CI, 6.18–70.98) [25-37]. With regard to the need for surfactant re-treatment, the aforementioned review highlights that only one of the studies analyzed, provided data on this point, with a sensitivity of 84% and specificity of 70% [37].

There were significant differences between the groups of patients that did and did not require surfactant, especially in terms of GA and oxygenation parameters. This is to be expected, as it tends to be the most immature and critically ill neonates who typically need this treatment. In our sample, we compared the ROC curves of oxygenation (FiO2) and lung ultrasound with respect to surfactant administration. We found the curves to be similar; with optimal AUC values, but with even higher results for ultrasound. We did not use invasive methods to evaluate oxygenation because most preterm infants in our unit did not have an arterial catheter and, furthermore, current recommendations for treatment with endotracheal surfactant are still based on FiO_2 [29]. There is evidence to support the use of the S/F ratio for monitoring oxygenation in preterm infants and was comparable to the oxygenation index, but with the advantages of being noninvasive and providing constant information.

We found no differences when assessing ultrasound changes after administering surfactant, in line with the results of Copetti *et al*. [23] and Cattarossi *et al*. [38]. This is probably related to the fact that the treatment improves the alveolar component and therefore, the oxygenation. But does not modify or accelerate the removal of fluid from the interstitial space [38]. It may also be related to the short time elapsed between surfactant administration and the second lung ultrasound (2 h). It would be interesting to follow the evolution over the next few hours, as greater differences were found at 24 h after surfactant instillation. Some studies have described subtle differences, but these employed a more complex graduation than ours and approached the thorax in a combined trans-thoracic and trans-abdominal manner.

If these results are confirmed, with other findings, this tool could help in the selection of patients who would benefit from surfactant treatment. Further, neonatologists should receive training in lung ultrasound since, promising results are obtained even in NICUs with relatively less experience on this technique. Only a few patients received mechanical ventilation and two doses of surfactant, but we still observed some significant differences. However, future detailed study is needed on possible asymmetry in the lung ultrasound pattern due to the patient's position or the homogeneity of the white lung pattern with sub-pleural consolidations in all fields, as well as the development of bronchopulmonary dysplasia as per the early ultrasound pattern.

CONCLUSION

Early lung ultrasound in preterm infants with respiratory distress appears to be a useful tool with no adverse effects for the patient. It allows a better assessment of RDS by detecting patients with a greater risk of requiring surfactant or mechanical ventilation even before oxygenation criteria. We, therefore, recommend implementing protocol to train neonatologists in this field and include this as an additional tool to help assess these patients.

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