Original Article

Prospective investigation of serial ultrasound for transient tachypnea of the newborn

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Background: Transient tachypnea of the newborn (TTN), which is diagnosed using typical clinical course and radiographic findings, is the most common cause of respiratory distress in late-preterm and term neonates. Lung ultrasound (LUS) is increasingly used to identify TTN according to the distinct characteristics of the disease. However, few studies have reported the application of LUS to monitor the clinical evolution of TTN. Using serial LUS, this prospective study assessed and monitored TTN severity.

Methods: From November 2018 to October 2019, neonates ≥34 weeks of gestation admitted to the newborn center of Chang Gung Memorial Hospital were enrolled. Neonates diagnosed with TTN and requiring respiratory support comprised the TTN group (n = 29), whereas those without respiratory disease served as the control group (n = 23). LUS was performed and scored in both groups within 4 h of admission and followed up at 24 and 48 h.

Results: A total of 65 infants were screened for enrollment and 13 were excluded. Most of the enrollees in both groups exhibited a peak LUS score on the first day, which then gradually declined thereafter. In comparison with the control group, the LUS score of the TTN group was higher on day 1 and day 2, and it had a significantly greater decrease from day 1 to day 2. In the TTN group, LUS scores moderately correlated with respiratory severity scores.

Conclusion: We conducted a serial and quantitative LUS investigation in late-preterm and term infants with TTN. The LUS score mirrored the respiratory status relatively well, and it can help to monitor the clinical course of TTN, in the case of either resolution or deterioration.

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1. Introduction

After birth, fetal lung fluid is rapidly cleared to allow gas exchange. Impairment of this postnatal transition results in neonatal breathing difficulty. In late-preterm and term infants, transient tachypnea of the newborn (TTN) is the most common cause of respiratory distress, which results from inadequate lung fluid absorption. Currently, TTN diagnosis is mainly based on clinical course and typical findings on chest radiography, such as prominent peri-hilar vascular markings and fluid in the fissures.1

Lung ultrasound (LUS) is a noninvasive, bedside available, and radiation-free technique that has been widely used for the diagnosis of diverse neonatal respiratory conditions including TTN, respiratory distress syndrome (RDS), pneumonia, and other pulmonary diseases.1-3 LUS has been applied to monitor extrauterine lung fluid clearance during the early postnatal life.6 The presence of a double lung point is believed to be a specific and sensitive sign of TTN.7 Other ultrasound characteristics including lung alveolar-interstitial syndrome, compact B-line, and white lung are also considered accurate and reliable for the diagnosis of TTN and for differentiating TTN from RDS.8 Moreover, a LUS score can reportedly delineate the severity of lung disease more objectively.9

In clinical application, LUS has been used to predict noninvasive ventilation failure in a preterm population,10 to predict the need for respiratory support in term and late-preterm neonates according to three distinct LUS patterns and their shifting,9 and to evaluate oxygenation and surfactant administration in preterm infants treated with continuous positive airway pressure (CPAP).9

However, few studies have evaluated the use of sono- graphic imaging to monitor the clinical evolution of TTN in the first days of life. Thus, in this prospective study, we performed serial LUSs to more quantitatively assess the clinical evolution of TTN.

2. Methods

2.1. Study population

From November 2018 to October 2019, neonates born at ≥34 weeks of gestational age, admitted to the newborn center of Chang Gung Memorial Hospital, Linkou branch, were screened for recruitment in this study. Neonates with respiratory distress (tachypnea, nasal flaring, grunting, suprasternal and subcostal retraction, etc.) who were suspected of having TTN and required respiratory support in the form of nasal CPAP or exhibited more advanced ventilatory demands after birth were considered eligible for the TTN group, whereas those without any symptoms of respiratory disease were enrolled in the control group. Clinical decisions including ventilator setting were judged according to the local neonatal intensive care unit protocol. The diagnosis of TTN was confirmed 3 days after birth by an attending physician not involved in this study by using all the available information, which included clinical course, laboratory data, culture results, and chest radiography. Patients with an identified respiratory disease other than TTN were excluded.

Other exclusion criteria were as follows: (1) chromosomal abnormalities; (2) structural heart disease or other major organ malformations; (3) hydrops fetalis and/or congenital pleural effusion; (4) pneumothorax and/or pneumomediastinum; (5) perinatal asphyxia and/or receipt of therapeutic hypothermia; and (6) severe hemodynamic instability associated with sepsis or other causes. The Chang Gung Ethics Committee approved this study (Institutional Review Board number: 201701809B0), and written informed consent was obtained from the parents or legal guardians of the neonates.

2.2. Lung ultrasound

An LUS was performed in the supine position by a single skilled operator (C.H.L.) using an Acuson P300 machine (Siemens, Germany) equipped with a linear probe (10–12 MHz). The LUS was executed within 4 h of admission, with follow-up assessments 24 and 48 h later. Four transverse sections (anterior upper and lower and lateral upper and lower) of each hemithorax were examined in the same manner. Subsequently, the stored images were sent to a pediatric pulmonary specialist (S.H.L.), who was blinded to the clinical condition, for reviewing the images and defining the scores.11 On an LUS, a normal aerated lung is filled with horizontal repetition artifacts of the pleural line known as “A-lines;” fluid accumulation in the alveolar or interstitial space generates comet-tail, vertical artifacts known as “B-lines.”1,6 As illustrated in Fig. 1, the score we used was modified from that proposed by Brat et al.7 A score between 0 and 3 was assigned for each lung area, with the total score ranging from 0 to 24. A score of 0 was assigned if only A-lines were observed; that indicated a normal aerated lung. A score of 1 was assigned if 3 or more well-spaced B-lines were observed. Crowded B-lines were assigned 2 points, and coalescent B-lines or white lung were assigned 3 points. More lung interstitial and alveolar fluid content resulted in more abundant B-lines over the lung fields and, consequently, higher LUS scores.

2.3. Data collection

Demographic data including gestational age, birth weight, sex, delivery method, Apgar score at 1 and 5 min, and laboratory results, such as hemoglobin at the date of birth, were documented. In the TTN group, the ventilator setting
and associated respiratory severity score (RSS) were recorded to express the clinical severity and to compare with the LUS score at the same time point. RSS is a simplified severity score consisting of the mean airway pressure (MAP) multiplied by the fraction of inspired oxygen (FiO₂). We collected the first record of both MAP and FiO₂ after admission and those 24 and 48 h later, then we calculated RSS of the first 3 days. The oxygen index was not used in our study because arterial blood analysis was not obtained daily in all neonates.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS version 22 (IBM, Armonk, NY, USA). Clinical features, laboratory data, and the LUS score were reported using descriptive statistics (mean ± standard deviation for continuous variables and frequency distributions for categorical variables). In the TTN group and control group, continuous and categorical variables were compared using independent sample t tests and Pearson’s chi-squared test, respectively. The LUS score was analyzed using repeated measures analysis of variance and independent sample t tests, as appropriate. The correlation between the LUS score and RSS was analyzed using Pearson correlation coefficient. A p value of <0.05 was considered statistically significant.

3. Results

A total of 65 patients were eligible for this study. The TTN and control groups had 42 and 23 neonates, respectively. Fig. 2 illustrates the enrollment flowchart. All participants received LUS over 3 days as standard protocol. In the TTN group, 13 patients were excluded for the following reasons: 6 were diagnosed with RDS, 3 had congenital pneumonia, and the remaining 4 met at least one of the exclusion criteria. The remaining 29 patients proceeded to final analysis. All patients in the TTN group were weaned from noninvasive ventilation within 1 week except one male preterm (case no. 36: twin B, 34 weeks of gestational age, birth weight 3075 g) and none received surfactant treatment. Moreover, 5 patients were free of ventilatory support by 48 h of age. In the control group, no patients were excluded and most were admitted because of low birth weight (14/23, 61%) or newborn fever (4/23, 17%). Basic demographic data are summarized in Table 1. No significant difference was observed between the two groups in terms of demographic characteristics. The time from birth to the first LUS is not significantly different in both groups.

Sequential scans revealed an LUS score trend for each group. In both groups, the LUS scores decreased significantly from day 1 to day 2 (p < 0.001; Fig. 3A). The TTN group exhibited significantly higher LUS scores than did the control group on day 1 (9.7 ± 3.9 vs. 4.0 ± 2.1, respectively, p < 0.001) and day 2 (4.0 ± 3.3 vs. 1.7 ± 1.2, p < 0.05), but the difference did not reach significance on day 3 (2.7 ± 3.2 vs. 1.4 ± 1.4, p = 0.065). Fig. 3B reveals the decline of the LUS score in both groups. In comparison with the control group, the LUS score of the TTN group had a significantly greater decrease from day 1 to day 2 (p < 0.01).

We collected the LUS score and RSS for the first 3 days. A moderate correlation was observed between the LUS score and RSS of the same day, which indicates that the LUS score reflects the clinical respiratory severity of neonates diagnosed with TTN (Fig. 4). The correlation coefficient was 0.494 (p < 0.001).

4. Discussion

TTN is the most common respiratory illness in newborns and affects some term and late preterm infants. Promptly distinguishing it from other severe lung conditions facilitates appropriate treatment. LUS is increasingly used to identify respiratory illness and guide clinical intervention in neonates. In this prospective study, we performed serial lung scans to assess and follow up TTN severity using quantitative LUS scores. We observed that the decrement of LUS scores in the first days of life was correlated with clinical respiratory stabilization of neonates with TTN.

Studies have employed different LUS findings for the diagnosis of TTN, such as double lung point, alveolar-interstitial syndrome, compact B-line, and white lung.7,8 However, these descriptive terms are more qualitative.
than quantitative in content. Brat et al. proposed a neonatal-adapted LUS score to describe and compare the severity of lung disease in a more objective manner. According to that LUS scoring system, the lung is divided into three areas (upper anterior, lower anterior, and lateral), and a score is assigned to each area ranging from 0 (the presence of only A-lines) to 3 (extended consolidation with air bronchograms). We modified the scoring system because pulmonary edema and compact B-lines rather than lung consolidation with air bronchograms are commonly observed in neonates with severe interstitial or alveolar edema. The lateral zone was divided into two areas for more precise quantification of interstitial edema of the dependent lungs.

In a study of 154 neonates with similar gestational age, Raimondi et al. described a gradual shift from hyperechoic lung profiles to the predominance of A-lines in most neonates within 36 h of birth. In another study by Liu et al., the degree of pulmonary edema decreased gradually during the convalescence phase of patients with TTN. Similar to the aforementioned result, our study revealed that the serial LUS score declined gradually after birth, irrespective of pulmonary condition. This reflects the physiological occurrence of fetal lung fluid absorption in the immediate extrauterine life.

In comparison with neonates without respiratory disease, the LUS score of those with TTN was significantly higher in the first 2 days of life. Delayed or halted fetal lung
fluid clearance was indicated by coalescent B-lines or white lung. The affected neonates frequently developed respiratory distress due to pulmonary edema. The present study displayed an early ultrasonic difference between patients with TTN and those without respiratory illness in a quantitative manner.

With appropriate respiratory support, our study indicated that the LUS score of most neonates experiencing TTN drastically decreased between the first and second day of life. This decrease also coincided with the clinical resolution of respiratory distress (improved breathing pattern without the need for intubation) and improvement in chest radiography results (if repeated).

In our study, the scores of serial LUS measurements correlated well with the clinical respiratory condition (i.e., RSS) in the TTN group. Most LUS scores in the TTN group gradually decreased except for one male preterm infant (case no. 36). He was initially responsive to noninvasive ventilation support but his condition deteriorated; he was subsequently intubated at 2 days of age. Neither his LUS score nor his RSS decreased from day 1 to day 3, which was contrary to expectations. His diagnosis was still considered as TTN because he had a similar initial presentation as the other enrollees in the TTN group. His chest radiography did not reveal patchy or asymmetrical opacities nor a diffuse ground glass appearance. No prenatal risk factor, neonatal infection, or cardiac anomaly was found in the later workup. Because TTN is considered a disease involving multiple factors, including impairment of fetal lung fluid reabsorption and surfactant abnormalities, his distinct clinical manifestation might have resulted from both unresolved interstitial edema and a certain degree of surfactant deficiency. This neonate’s initial TTN might have been later superimposed with RDS or another respiratory disease, which is another explanation for his condition.

Therefore, a distinct trend in the LUS score might help to identify infants with an atypical clinical course of TTN (namely prolonged ventilation demand), which warrants further investigations.

In this study, we revealed that the LUS score mirrored the clinical respiratory severity relatively well, either during the convalescence phase or during progression. Although operator-dependent bias was minimized by using only one LUS operator, we acknowledge some other limitations in this study. First, the sample size was relatively small. For a more consistent result, further studies including more patients are required. Second, the operator who performed the ultrasound scan was not blinded to the clinical condition of the enrollees. Nonetheless, the fact that the LUS scorer was unaware of relevant clinical data likely diminished this observation bias. Third, TTN is typically diagnosed clinically, not pathologically, because it is difficult to differentiate it from other interstitial lung diseases that mimic the clinical presentation of TTN. It further hints at the delayed resolution of ultrasonic findings warranting to consider diagnoses other than TTN.
LUS is a real-time, noninvasive tool that minimizes patients’ exposure to radiation, discomfort, and transportation within the hospital. Thus, it can be used for initial screening, dynamic follow-up, and therapeutic evaluation. In this study, we revealed that the results of serial LUSs were consistent with the clinical status of respiration in infants with TTN. The LUS can help to monitor the clinical course of TTN, in the case of either resolution or deterioration.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

References