Evaluation of Surfactant Replacement Therapy Effects – A New Potential Role of Lung Ultrasound

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SUMMARY

Introduction Previous studies suggested that effects of the surfactant administration in preterm infants with respiratory distress syndrome cannot be followed by lung ultrasound (L-US).

Objective The aim of the paper is to evaluate the surfactant replacement therapy effects using a new, proposed grading system for L-US findings.

Methods We report the series of 12 preterm infants with clinical and radiographic signs of respiratory distress syndrome, in whom L-US examinations were performed prior to, and within the first 24 hours after surfactant administration. To evaluate the surfactant replacement therapy effects, we proposed a new grading system (1 to 6) for L-US findings at each examined lung area, based on the presence of normal finding, the amount of B-lines and subpleural consolidations.

Results All preterm infants had an improvement of L-US findings from one to four grades observed within the first 24 hours after surfactant administration, which has not been previously reported. The improvement of L-US findings was most commonly observed in anterior lung areas.

Conclusion L-US might enable an early detection of the surfactant replacement therapy effects. Further prospective studies are necessary to define the role of L-US in this field.

Keywords: respiratory distress syndrome; premature; ultrasound; lung; surfactant

INTRODUCTION

Of the many complications of prematurity (intracranial hemorrhage, necrotizing enterocolitis, sepsis, and retinopathy), lung diseases remain the most common cause of neonatal morbidity. Respiratory distress syndrome (RDS) is one of them, and presents the clinical expression of surfactant deficiency in neonates [1].

Administration of exogenous surfactant after delivery improves oxygenation, decreases the need for mechanical ventilation, and reduces mortality in neonates with RDS. The effects of surfactant replacement therapy are commonly followed up using chest X-rays (CXRs) [1].

Although lung ultrasound (L-US) in children has already been recognized as a potentially useful diagnostic modality, it is not, at present, frequently used in detection and follow-up of neonatal respiratory diseases [2-10]. There have been just a few studies dealing with application of L-US in this field [11-19].

OBJECTIVE

The aim of this study was to evaluate surfactant replacement therapy effects using a new, proposed grading system for L-US findings.

METHODS

A prospective study was carried out in association with the Neonatal Intensive Care Unit (NICU) and the Radiology Department. The inclusion criteria were both clinical and radiographic signs of RDS, gestational age (GA) under 37 weeks, and administration of surfactant performed in our NICU.

The study included 12 preterm infants (six males and females). GA was ranging from 29 to 36 weeks of gestation. The average GA of patients was 32.83 weeks of gestation (SD=2.84). The birth weight of patients ranged between 1,190 g and 3,280 g (mean value 2,216.7 g, SD=875.9).

Out of 12 premature infants four received prenatal corticosteroids. Four infants were born vaginally, while eight were delivered by C-section. Porcine exogenous surfactant (Curosurf, Chiesi Pharmaceutical, Parma, Italy) was endotracheally administered in all patients at the average time of 8.1 hours (SD 3.53 hours). Mechanical ventilation was required in each preterm infant, with mean duration of mechanical ventilation being 4.17 days (SD 2.04 days).

The Ethical Committee approved the research and informed consent was obtained from the parents of each examined preterm infant.

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L-US was performed in all infants just before and within the first hour after surfactant administration, as well as within the first 20 to 24 hours of surfactant application. All the L-US examinations were performed by one experienced pediatric radiologist (J.L.) in supine, as well as in right and left lateral decubitus positions, using a 7.5 MHz linear probe (Sonoline Adara, Siemens, Erlangen, Germany). Due to their clinical conditions, all the preterm infants were examined in incubators. The radiologist was blinded to the CXR and clinical findings of each preterm infant. CXRs were reported by other experienced pediatric radiologists of the department, apart from J.L. The clinical condition of each infant was estimated by an experienced neonatologist (A.D.). The double lung point sign, characteristic of transient tachypnea of the newborn, was ultrasonographically excluded in each patient as a possible cause of respiratory distress [15].

L-US examinations were performed using both trans-thoracic and trans-abdominal approach. The trans-thoracic US approach included examination of the anterior (between the sternum and the anterior axillary line), lateral (between the anterior and posterior axillary lines) and posterior (between the posterior axillary line and the spine) lung areas in caudocranial direction. Anterior and lateral lung areas were evaluated in supine position, while posterior lung areas were examined in lateral decubitus positions. The trans-abdominal US included the trans-hepatic and trans-splenic approach to examine both lung bases in supine position of the patient.

These two US techniques provided division of each hemithorax into four lung areas, i.e. eight lung areas per patient. The right lung base was examined by trans-hepatic approach, while right anterior, lateral, and posterior lung areas were examined by trans-thoracic approach. The left lung base was examined by trans-splenic approach, and trans-thoracic approach was used to examine left anterior, lateral and posterior lung areas. Longitudinal and transverse (intercostal) sections were used in the trans-thoracic examinations of each lung area. Oblique transverse sections were mostly used for the trans-hepatic approach, whereas oblique longitudinal sections were used for the trans-splenic approach.

Normal L-US findings

The pleura is trans-thoracically visualized as a smooth, echogenic line, whose thickness is normally up to 0.5 mm [16]. The evaluation of the pleura also includes the "lung sliding" sign, which represents the sliding of the visceral pleura over the parietal pleura [9].

Underneath the pleura are the lungs, filled with air, which disables the visualization of the lung parenchyma. However, horizontal artifacts resulting from the high acoustic impedance between the visceral pleura and the lung parenchyma are seen, and are called A-lines – the parallel echogenic lines below the pleural line, equally distanced from one another (Figure 1) [20, 21]. If the US examination of the lung bases is performed using the trans-abdominal approach, with the liver or spleen forming the acoustic window, it is normally based on the acoustic phenomenon of "mirror image," which is a supra-diaphragmatic projection of the liver or spleen [11, 22].

Pathological L-US findings

When the parenchymal disease propagates to the pleura, an acoustic window is formed and this creates a transmission of an ultrasound beam, enabling the evaluation of lung tissue. The absence of alveolar air in the lung periphery is visualized as a hypoechogenic area, representing the subpleural consolidation (Figure 2) [10].

Figure 1. Normal lung ultrasound finding using the trans-thoracic approach in a transverse (intercostal) section

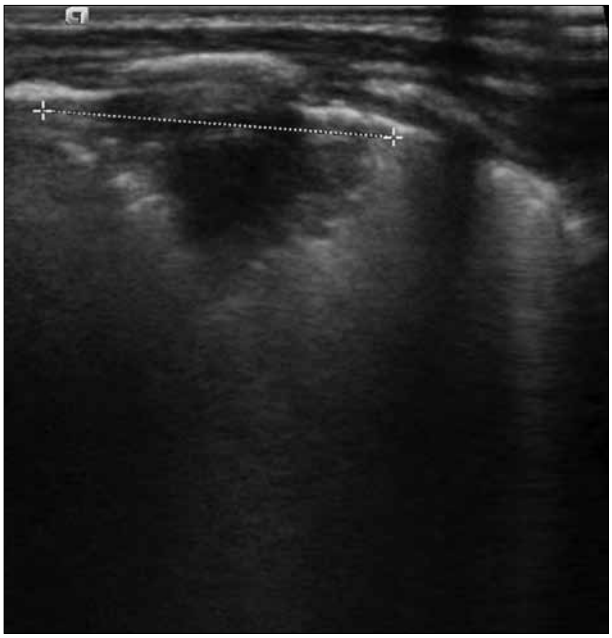

Figure 2. Subpleural consolidation (marked with asterisks) using the trans-thoracic approach

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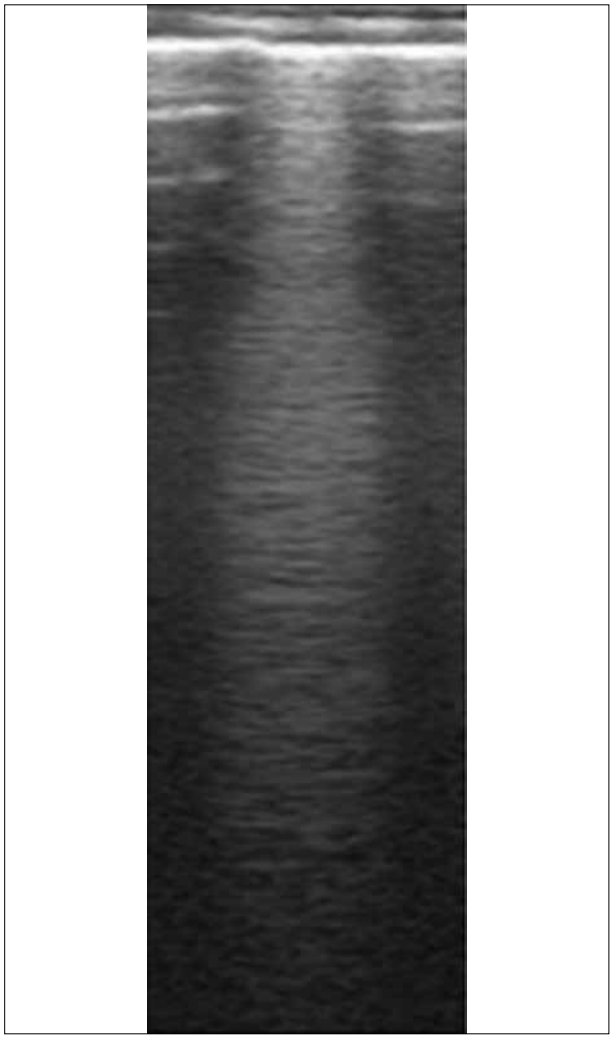

Figure 3. B-line

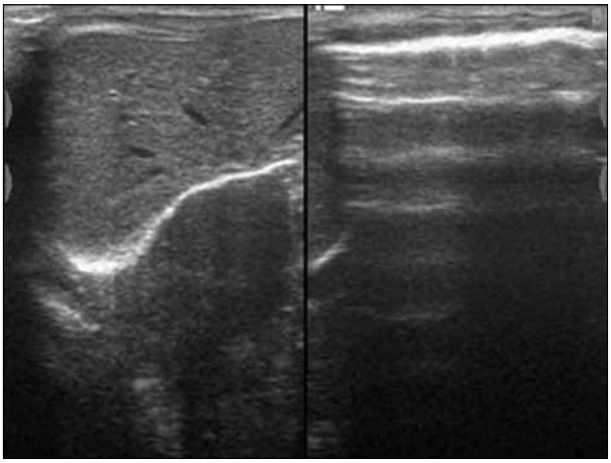

Figure 4. Normal lung ultrasound finding trans-hepatically ("mirror image" phenomenon, left image), and trans-thoracically (right image), on longitudinal section

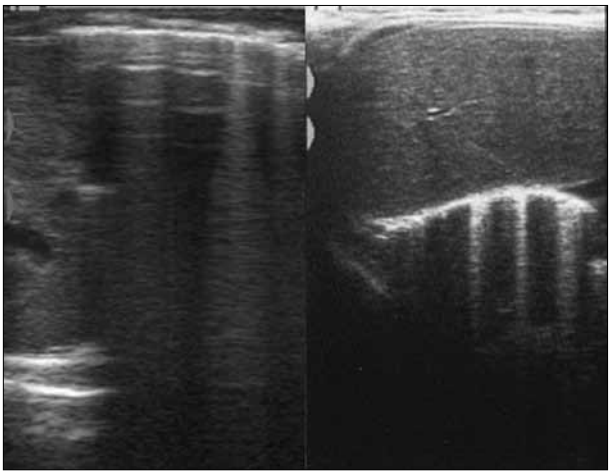

Figure 5. Grade 2, using the trans-thoracic (left image) and the trans-hepatic approach (right image)

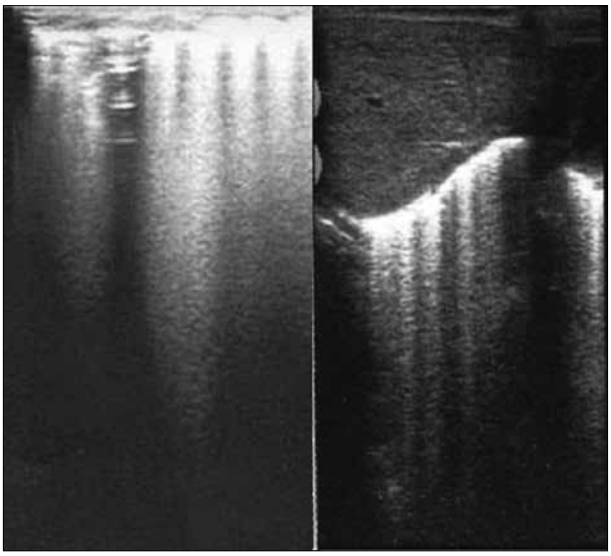

Figure 6. Grade 4, using the trans-thoracic (left image) and the trans-hepatic approach (right image)

The presence of the vertically oriented "comet tail" artifacts in the lungs, called B-lines, is a result of the accumulation of fluid in the subpleural interlobular septa surrounded by air [23]. B-lines extend from the pleural line to the bottom of the screen. They are hyperechogenic, sharply defined, erase the A-lines, and move with "lung sliding" (Figure 3). Depending on the amount of B-lines, the interstitial edema (B-lines combined with "spared" areas of normal L-US finding) and alveolar-interstitial edema (compact pattern of B-lines) can be recognized [23].

Grading system of L-US findings

In order to provide more precise and adequate evaluation and classification of L-US findings, the following grading system has been applied for each examined lung area, using the longitudinal section in the trans-thoracic approach, and oblique transverse and oblique longitudinal sections in the trans-abdominal approach. Grade 1 stands for a normal finding (Figure 4). Grade 2 stands for a distribution of B-lines in less than 50% of the visualized lung area (Figure 5). Grade 3 stands for a distribution of B-lines within the half of the lung area, whereas their distribution over 50% corresponds with grade 4 (Figure 6). Grade 5 stands for a compact pattern of B-lines which extend through the whole lung area (Figure 7). The worst finding, graded 6,

Figure 7. Grade 5, using the trans-thoracic approach

presents with subpleural consolidation in the lung area, regardless of the relation between A- and B-lines.

Based on the proposed L-US grading system, L-US findings in all infants were compared before surfactant administration, and within the first hour and 20–24 hours after surfactant administration at each examined lung area. In preterm infants with CXRs performed before and within 24 hours after surfactant application, the comparison between L-US and CXR findings was made. In each infant the number of lung areas with regression of L-US finding was recorded, and the lung areas with the highest frequency of improvement of L-US finding were detected.

RESULTS

During the first hour after surfactant administration, in eight out of 12 patients the regression of L-US findings in at least one lung area was detected, showing an improvement of one to two grades. An improvement of up to four grades, in relation to initial examination prior to surfactant administration, occurred in all infants between 20 and 24 hours after surfactant application at one or more lung areas. In preterm infants with CXRs performed before and within 24 hours after surfactant application, the improvement of L-US findings was consistent with improvement of the CXR findings (Figures 8, 9 and 10).

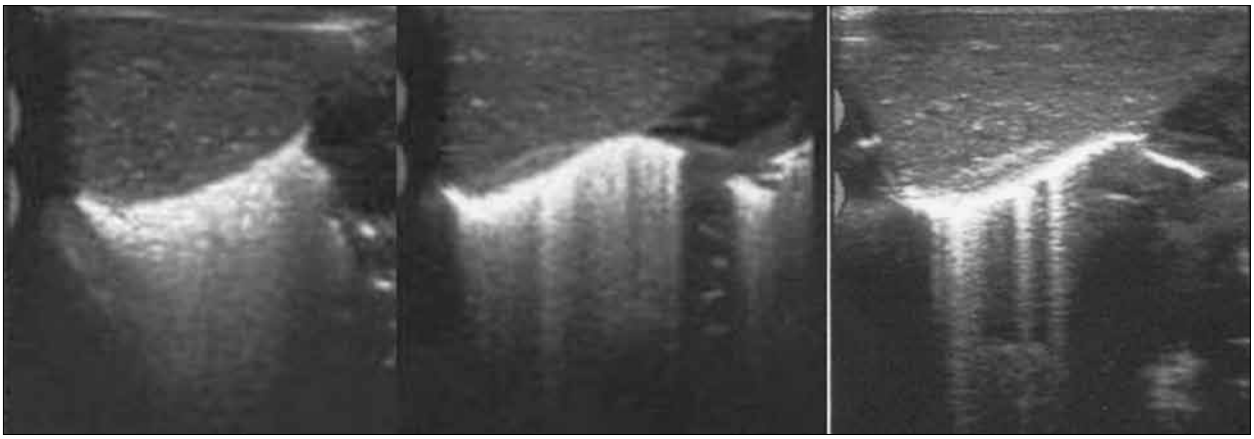

Figure 8. Change of the US finding at the right lung base, using trans-hepatic approach, from a grade 6 (prior to surfactant administration, left image), over a grade 4 (0.5 hours after surfactant administration, image in the middle), to a grade 2 (22 hours after surfactant application, image to the right)

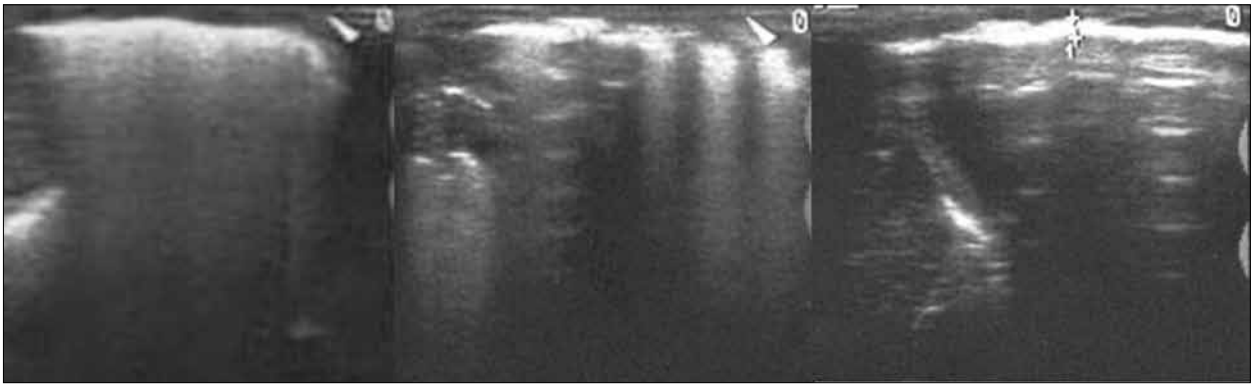

Figure 9. Change of the US finding at the anterior left lung area (trans-thoracic approach) from a grade 5 (prior to surfactant administration, left image), over a grade 3 (0.5 hours after surfactant administration, image in the middle), to a grade 1 (22 hours after surfactant application, image to the right)

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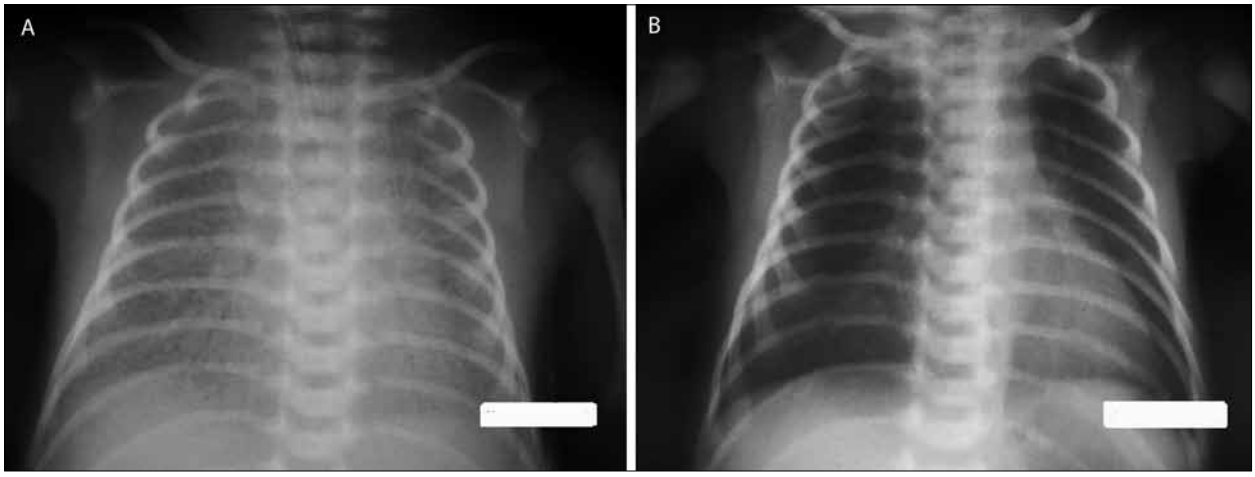

Figure 10. Chest X-ray findings in the same child as in the Figures 7 and 8 just before (A) and 22 hours after (B) surfactant application. A – respiratory distress syndrome (RDS), B – significant regression of RDS signs

Table 1. The number of preterm infants with an improvement of lung ultrasound finding at examined lung areas within the first 24 hours after surfactant administration

Lung area	H	Ar	Lr	Pr	S	Al	Ll	Pl
Preterm infants	4	10	4	6	2	6	8	6

H – trans-hepatic approach to the right lung base; S – trans-splenic approach to the left lung base; trans-thoracic approach to the: Ar – anterior right, Al – anterior left, Lr – lateral right, Ll – lateral left, Pr – posterior right, Pl – posterior left lung areas

In four preterm infants an improvement of the L-US findings was observed in one lung area within the first 24 hours after surfactant application, whereas the regression of L-US findings visualized at three, four, six and all eight lung areas was equally distributed throughout the remaining eight infants (two per each).

The improvement of L-US findings was most commonly observed in anterior lung areas (right and left) – 16 times, followed by lateral and posterior lung areas – 12 times both (Table 1).

DISCUSSION

The application of L-US in preterm infants with RDS has so far been evaluated only in a small number of studies [11, 13, 16, 17, 18]. In some of these studies the trans-abdominal approach was used exclusively [11, 13], but the major step forward seems to be the introduction of the trans-thoracic approach in newborns with transient tachypnea in the Copetti and Cattarossi's [15] study. It allowed evaluation of all the lung areas, and not only the bases, and was later applied for the first time in the diagnosis of RDS by Copetti et al. [16]. This study showed no significant changes of L-US findings in preterm infants before and after the administration of surfactant in the first 48 hours of life [16]. These results were further confirmed by animal experiments [17]. In one study L-US examinations were performed using the combination of the trans-thoracic and trans-abdominal approach [18].

Our everyday experience showed that although the lung bases could be in most cases adequately visualized using the trans-thoracic approach, with a certain number of patients the US findings on the lung bases were clearer and more precise when using the trans-abdominal approach. Therefore, we performed each L-US examination using a combined US technique, i.e. using both the trans-thoracic and trans-abdominal approach. The need to grade US findings in each lung area emerged. Up to now, the US findings in the lungs were distinguished as normal, interstitial edema, alveolar-interstitial edema and subpleural consolidation, or divided into the three types, as in the study of Raimondi et al. [16, 19, 23]. In order to establish an easily applicable and more precisely defined grading of L-US findings, we proposed the new grading system ranging from 1 to 6, where grade 1 presented a normal finding and grade 6 the subpleural consolidation. The grades from 2 to 5 depended on the ratio between the B-lines and the "spare areas" of normal L-US finding defined by the horizontal A-lines.

Even though previous studies suggested that the administration of surfactant in preterm infants with RDS does not affect the interstitial compartment and lung water clearance [16, 17], we showed the improvement of L-US findings in each of the 12 preterm infants within the first 24 hours after application of the same type of exogenous surfactant (Curosurf) as in the study by Copetti et al. [16]. In four preterm infants, this improvement was observed in only one lung area, but in the rest of the infants it was detected in three and more lung areas, in two patients even in all eight of them. The most common was an improvement of L-US findings in anterior lung areas (right and left).

We can only hypothesize about the reasons of regression of L-US findings. Sometimes an improvement was very subtle, especially within the first hour after surfactant administration. We think that the proposed grading system gives the ultrasonographer an opportunity to observe even some discreet changes, which may easily go undetected. The most frequent improvement of L-US findings in anterior lung areas might be the result of mostly supine position of preterm infants in incubators, which might enable the fastest interstitial fluid clearance due to the force of gravity, opposed to the reduced ventilation in the pos-

terior lung areas. Also, our results might indicate the need to reconsider the standpoint that surfactant administration in preterm infants affects only the alveolar space, and not the interstitial compartment [16, 17]. The use of L-US in monitoring surfactant replacement therapy effects might also have a potential to reduce the number of CXRs in NICUs, and decrease the dose of ionizing radiation preterm infants are exposed to.

Our study has certain limitations. Even though blinded for the CXR and clinical findings prior to each US examination, a single experienced pediatric radiologist performed and evaluated all L-US examinations. However, the issue of inter- and intra-observer variability in the interpretation of L-US findings is reported to be significantly less relevant compared to the CXR findings [16, 24]. On the other hand, it is reasonable to hypothesize that similar results might not be immediately achieved by less experienced operators. The number of preterm infants included in the study was small. We took into consideration only the patients who had surfactant administered in our NICU, and not at the maternity hospital or during the transport to our hospital, as that was the only way to ultrasonographically examine infants before and after surfactant application. This is the reason why the average time of surfactant application in our study was rather late.

CONCLUSION

This study revealed the potential of ultrasound in monitoring the effects of surfactant replacement therapy, which has not been reported so far. Further, more extensive, prospective studies are necessary to define the role of L-US in this field.

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Процена ефеката терапије сурфактантом – нова потенцијална улога ултразвука плућа

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КРАТАК САДРЖАЈ

Увод Претходно објављене студије су показале да се ефекти терапије сурфактантом код претерминске новорођенчади с респираторним дистрес синдромом (РДС) не могу пратити помоћу ултразвука плућа (УЗП).

Циљ рада Циљ рада је био да се процене ефекти лечења сурфактантом код недоношчади са РДС користећи нови предложени систем степеновања налаза УЗП.

Методе рада Студија је обухватила 12 новорођенчади рођене пре термина с клиничким и радиографским знацима РДС код којих је УЗП био начињен пре и у прва 24 часа након примене сурфактанта. Да бисмо оценили ефекте терапије сурфактантом, предложили смо нови систем степеновања (1–6) за налазе УЗП у свакој прегледаној плућној зони који је заснован на постојању нормалног налаза, субплеуралних консолидација и заступљености Б линија.

Резултати Код све претерминске новорођенчади уочено је побољшање налаза УЗП од једног до четири степена током прва 24 часа од примене сурфактанта, што досад није објављено. Побољшање налаза УЗП је најчешће било видљиво у предњим регијама плућа.

Закључак УЗП може да омогући рано откривање ефеката терапије сурфактантом. Неопходно је урадити нове проспективне студије које би јасно дефинисале улогу УЗП у овој области.

Кључне речи: синдром респираторног дистреса; прематурус; ултразвук; плућа; сурфактант

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