CHEST RADIOLOGY

Role of transabdominal ultrasound of lung bases and follow-up in premature neonates with respiratory distress soon after birth

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Abstract

Background: Chest radiography has been the traditional method of diagnostic evaluation of patients of hyaline membrane disease (HMD). Lung sonography (USG) has been lately explored as an alternative modality. **Aims:** To explore the application of transabdominal USG of lung bases (TASL) in the evaluation of HMD in premature neonates with respiratory distress soon after birth. **Settings and Design:** Tertiary care institutional setup. Study duration–18 months. Follow-up–variable, up to 1 month. Prospective descriptive study. **Materials and Methods:** Eighty-eight consecutive patients admitted in the neonatal intensive care unit (NICU) with gestational age <32 weeks having respiratory distress within 6 h of birth were enrolled. The diagnosis of HMD was made if the patient had negative gastric shake test and/or suggestive chest radiograph. TASL was performed in all patients within the first 24 h of life and biweekly subsequently. USG was interpreted as normal, HMD pattern, or broncho-pulmonary dysplasia (BPD) pattern. Biweekly follow-up was done for patients showing HMD till normalization of the sonographic HMD pattern, development of the sonographic BPD pattern, or death/discharge of the neonate from the hospital. **Results and Conclusions:** TASL showed 85.7% sensitivity, 75% specificity, 88.88% positive predictive value, and 69.2% negative predictive value for the diagnosis of HMD. The abnormal sonographic findings on day 14 had 94.1% accuracy for prediction of eventual occurrence of clinical BPD. TASL is complementary to chest radiograph in the diagnosis of HMD. It is also useful for the early prediction of BPD with the potential of reducing the cumulative radiation dose to these neonates.

Key words: Hyperechogenicity; neonates; respiratory distress syndrome; transabdominal; ultrasound

Introduction

Hyaline membrane disease (HMD) (synonymous with respiratory distress syndrome) is primarily a disease of premature infants born before 32nd week of gestation.[1] Its incidence is close to 60% in babies born at or before 29 weeks of gestation.[2] Oxygen therapy along with surfactant supplementation currently forms the cornerstone of treatment for HMD. Excess of oxygen, however, may lead to toxicity, which along with persistent barotrauma can cause bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) in these babies.[3] Chest radiography has been the traditional method in the diagnosis and follow-up of children suffering from HMD.[4-7] Recently, few studies have shown promising results for transabdominal USG of the lung bases (TASL) in the diagnosis and follow-up of patients of HMD and for the early prediction of BPD.[8-11] The present study was devised to explore the application of TASL in the evaluation of HMD in premature neonates with respiratory distress soon after birth and for the early prediction of BPD.

Materials and Methods

This was a prospective descriptive study conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary care

hospital after obtaining approval from the institutional ethics committee. Neonates with gestational age less than 32 completed weeks who were admitted in the NICU with respiratory distress within 6 h of life were enrolled over 1 year 6 month duration. Written informed consent was obtained in all cases.

Gastric aspirate shake test (GST)[12] and portable chest radiograph was done on the day of admission/in the first 24 h in all the neonates. GST is based on the fact that gastric aspirate in a newborn infant consists mainly of swallowed lung fluid (source of surfactant) and amniotic fluid. The test involves thoroughly mixing equal amounts (0.5 ml each) of gastric aspirate taken within 30 mts of birth and normal saline and shaking the resultant solution with 1 ml of 95% alcohol. Absence of bubbles on the surface of the mixture is considered negative and indicates that the infant's lungs are immature making him/her at high risk of developing HMD. If bubbles are present on the surface of the fluid, then the test is positive and indicates that the lungs are mature and producing adequate amounts of surfactant making the infant less prone to develop HMD.The final diagnosis of HMD was made in accordance with the standard criteria defined at the National Neonatology Forum which is adopted by our institute,[13] according to which HMD is labeled when a neonate develops respiratory distress within 6 h of birth with either a negative GST or suggestive chest radiograph findings (viz. poor expansion with air bronchogram or reticulogranular pattern or ground-glass opacity).

All the patients underwent USG examination of the lung bases through a transabdominal approach on an HDI 3500 [Advanced Technologies Laboratories (ATL) Ultrasound, Bothell, WA, USA] USG scanner within the first 24 h of life. A pediatric multifrequency (5-12 MHz) curvilinear probe was used and the test was performed by a single radiologist. Both transhepatic and transsplenic windows were employed for scanning on both sides via a subcostal approach. The sonographic patterns were categorized as below in accordance with previously published studies:[8,10]
Normal pattern: Consisting of normal diaphragm echo complex with no retrodiaphragmatic hyperechogenicity [Figure 1A]
HMD pattern: Consisting of diffuse retrodiaphragmatic hyperechogenicity completely replacing the normal diaphragm complex [Figure 1B]
BPD pattern: Corresponding to the same hyperechogenicity as that of the HMD pattern, but less diffuse and less homogeneous [Figure 1C]. The neonates showing sonographic HMD pattern were followed up with serial biweekly sonographic examinations for studying the evolution of the sonographic features. The end point of the follow-up was the return of the HMD pattern to normal, development of BPD pattern on USG, or death/discharge of the neonate from hospital. Patients developing sonographic BPD pattern were evaluated once again after 3 days.
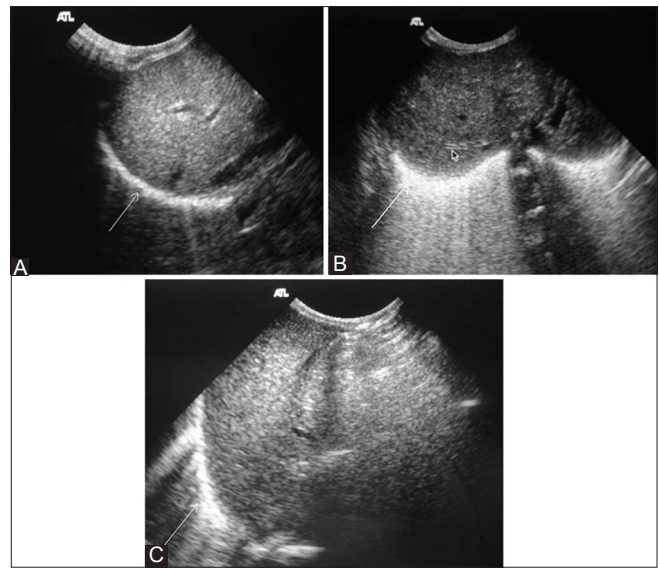

Figure 1 (A-C): TASL in newborn infants shows normal diaphragm echo (white arrow) complex–normal pattern (A), diffuse retrodiaphragmatic hyperechogenicity (white arrow) replacing the normal diaphragm echo complex–HMD pattern (B), and streaky retrodiaphragmatic hyperechogenicity (white arrow) replacing the normal diaphragm echo complex–BPD pattern (C)

Based on the findings of initial and serial sonographic examinations, the patients were categorized into the following groups:

Group 1: No sonographic HMD pattern seen on initial ultrasound

Group 2: Patients with HMD pattern on initial sonograms that showed complete resolution of retrodiaphragmatic hyperechogenicity on subsequent examinations

Group 3: Patients with HMD pattern on initial sonograms that showed partial resolution of retrodiaphragmatic hyperechogenicity on subsequent examinations and development of the BPD pattern

Group 4: Patients with HMD pattern on initial ultrasound that dropped out from the study due to death or discharge from the hospital. The diagnostic performance of TASL in the diagnosis of HMD and BPD was calculated. Clinical diagnosis of BPD was made if there was oxygen dependency at 28 days of life.[3] The earliest day when sonographic findings were predictive of the eventual outcome to clinical BPD with high accuracy was determined. During the course of the study, no interference, based on sonographic findings, was made with respect to the appropriate recommended interventions (e.g., surfactant administration) in these neonates, i.e., all the patients received standard of care therapy irrespective of the ultrasound findings.

Sample size calculation
Assuming the expected frequency of the retrodiaphragmatic hyperechogenicity in HMD to be 75% and that this sign will

not be seen in more than 35% of babies with respiratory distress due to other causes, we needed to study 24 babies each of respiratory distress due to HMD and non-HMD causes for $\alpha = 0.05$ and $\beta = 0.20$.

Results

During the period of enrollment, 97 neonates of less than 32 completed weeks who developed respiratory distress soon after birth were admitted in the NICU. Nine were excluded due to various reasons (consent not obtained in four, sonographic examination performed after 24 h of life in two, and absent gastric aspirate in three patients). Eighty-eight patients were eventually included in the study group.

Demographic data, results of GST, and the details of surfactant administration are summarized in Table 1. GST was done in 55 patients while it could not be performed in 33 patients due to reasons like non-aspiration of adequate amount of fluid, bloody aspirate, etc. GST was positive in 30/55 patients [Table 1].

Based on the standard clinicoradiographic diagnostic criteria[4], final diagnosis of HMD was made in 38 patients. 36/38 of these patients showed features of HMD on chest radiography. Forty-three patients received surfactant as part of treatment; 30 before and 13 after the USG examination.

Sonographic evaluation of the lung bases through the transabdominal route was done at admission between 4 and 20 h (mean 12 ± 3 h) in all the patients. Of the 88 patients scanned, fifty (56.8%) patients showed normal ultrasound on the day of admission, while 38 (43.2%) patients showed an "HMD pattern." Amongst the 38/88 actual HMD patients, TASL revealed an HMD pattern in 32 patients. In the remaining 50 (56.8%), TASL revealed a normal pattern in 44 patients and an HMD pattern in 6 patients. Three of the six false-positive cases had transient tachypnea of newborn [Figure 2] and another three had pneumonia. There were six false-negative cases. Thus, TASL had a sensitivity of 84.2%, specificity of 88%, positive predictive value of 84.2%, negative predictive value of 88%, and an overall accuracy of 86.4% in the diagnosis of HMD.

Of the two actual HMD patients in whom chest radiograph (CXR) was normal, GST scored over CXR meaning that it identified two additional patients who were declared non HMD on CXR. Out of the 38 sonographically labeled HMD patients who were followed up biweekly, 4 died while 1 left against medical advice on the insistence of the parents. Thirty-three neonates were eventually followed up sonographically. Of these 33 patients, 24 patients transformed to a normal pattern at various intervals ranging from 7 to 17 days [Figure 3] with no BPD pattern in the intervening period. In the remaining nine patients, the initial HMD pattern was replaced by a BPD pattern variably from 4 to 17 days of life. Three days after conversion to sonographic BPD pattern, follow-up USG revealed a normal pattern in three of them. These three infants showed complete clinical recovery with no evidence of BPD and were labeled as HMD in the final analysis. In the remaining six patients who showed persistence of the BPD pattern on the follow-up USG [Figure 4, Table 2], all eventually developed clinical BPD.

Thus, there were 27 patients who had shown HMD pattern on initial ultrasound with complete sonographic resolution during follow-up, majority (26, 96.2%) by day 14 of life. Also on this day, all the patients who eventually developed BPD showed abnormal sonographic findings, which included an HMD pattern in two patients and a BPD pattern in four patients. The accuracy of abnormal sonographic findings (i.e., either sonographic BPD or HMD pattern) for the prediction of clinical BPD was 18%, 18%, 48.1%, 61.5%, and 94.1% on days 1, 4, 7, 10, and 14, respectively. Thus, the 14th day of the life was the earliest day when clinical BPD could be sonographically predicted with high accuracy. The diagnostic performance of TASL in our study was comparable with previously reported studies [Tables 3 and 4].

Discussion

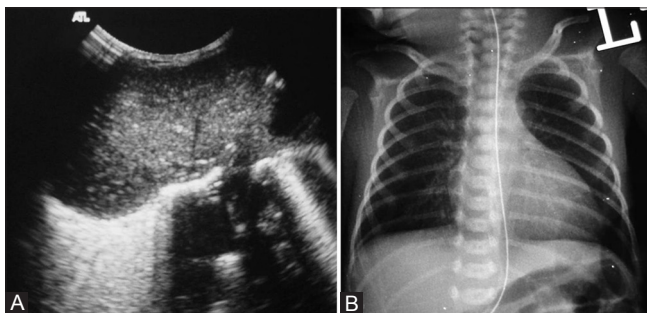Serial chest radiographs which currently form the basis of HMD

Figure 2 (A, B): An 8-h-old boy born at 30 weeks of gestational age having respiratory distress soon after birth. Axial TASL (A) shows an HMD pattern. Chest radiograph (B) taken on day 1 was normal. Gastric shake test was negative. Respiratory distress was relieved within 24 h and final diagnosis of transient tachypnea of new-born was made

Table 1: Demographic data, shake test results, and details of surfactant administration

Number of patients	88 (50 males, 38 females)
Gestational age	Average: 29+6 weeks ±11 days
	Range: 25+2–32 weeks
Body weight	Average: 1113 ±140 g
	Range: 700-1582 g
Gastric shake test	Negative: 25 (0 and +1)
	Positive: 30 (2+, 3+, 4+)
	No aspirate: 04
	Bloody aspirate: 02
	Not done: 27
Surfactant administration	
No. of patients	43 (Single dose: 34; two doses: 09)
Total no. of doses	52

diagnosis and follow-up have their own restrictions of ionizing radiation and delayed results. GST is a reasonably accurate indicator for gauging surfactant requirement. It is, however, of limited value where gastric aspirate cannot be obtained or is contaminated. Because of these reasons, alternate noninvasive diagnostic modalities are desirable in the diagnostic algorithm of HMD. Ultrasound offers the advantage of easy bedside availability and lack of ionizing radiation. Avni and colleagues[8] were the first to suggest its role in the diagnosis of HMD and described the sonographic HMD pattern in 22/24 premature HMD babies. This pattern was absent in all the 16 others who did not have HMD. Similarly Bober *et al.*[9] performed ultrasound in 131 consecutive newborns with respiratory failure within first 24 h of life and reported 100% sensitivity and 92% specificity for retrohepatic/retrosplenic hyperechogenicity in diagnosis of HMD. However, the sonographic diagnostic

criteria used by these authors were slightly different from those used by earlier authors[8,10,11] and by us. In our study, TASL had a sensitivity of 84.2% and specificity of 88%, which is comparable to previously published studies[8,9] [Table 3]. TASL may be useful in quick detection of HMD, which may aid in immediate surfactant administration especially when immediate portable chest radiography is not feasible (e.g., in machine breakdown, power failure, nonavailability of technologist, etc.).

Pathophysiology of sonographic HMD pattern has been explained by Avni and colleagues.[8] According to them, in HMD patients all the distal airways are distended by air and the alveoli are collapsed, surrounded by oedematous interstitial tissue. The interface of the walls of these distal bronchi, air within them, collapsed alveoli and surrounding oedematous tissue produce strong linear echoes with reverberation artefacts leading to retrodiaphragmatic hyperechogenicity. Bober *et al.*[9] has referred to this principle as 'acoustic mirror image phenomenon' whereby the ultrasound waves transmitted across the tissues are prone to reverberation (reflection), refraction, dispersion and absorption depending on the tissue type, frequency of the ultrasound waves, the relationship between the size of the object, the orientation of the surfaces of an object in space and the acoustic resistance of the transmitting medium.

The role of ultrasound in the follow-up of HMD and early prediction of BPD has also been studied previously.[10,11] Avni and colleagues[10] predicted future BPD at day 18 of life while Pieper *et al.*[11] predicted it at day 9. Our data suggest an accuracy of 94.1% for prediction of BPD at day

Table 2: Groups based on initial and serial sonographic examination of neonatal lungs by transabdominal USG of the lung bases

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Group 1	No sonographic HMD pattern seen on initial ultrasound	50
Group 2	Patients with HMD pattern on initial sonograms who showed complete resolution of retrodiaphragmatic hyperechogenicity on subsequent examinations	27
Group 3	Patients with HMD pattern on initial sonograms who showed partial resolution of retrodiaphragmatic hyperechogenicity on subsequent examinations	06
Group 4	Patients with HMD pattern on initial ultrasound who dropped out of the study due to death or discharge from the hospital	05
Total		88
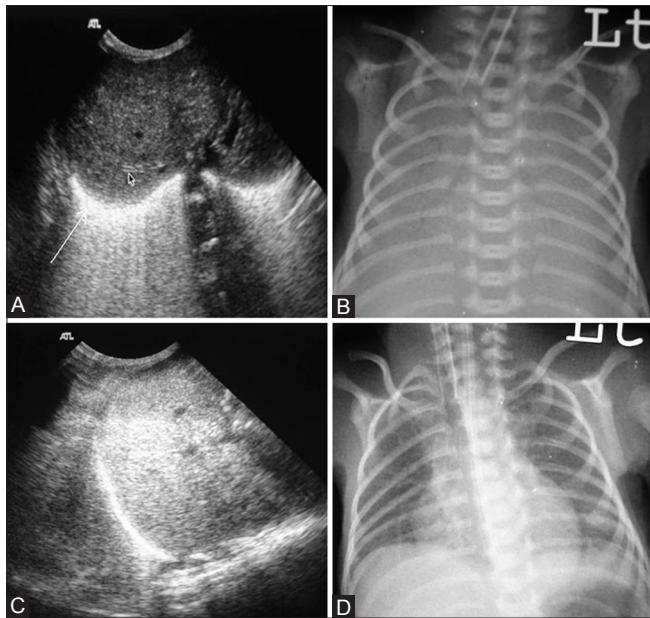
Figure 3 (A-D): A 6-hour-old girl born at 28+6 weeks of gestation having respiratory distress soon after birth. Axial TASL(A)) shows an HMD pattern. Corresponding chest radiograph (B) taken on day 1 showed bilateral whiteout lungs consistent with hyaline membrane disease. Coronal TASL (C) at day 14 showed resolution of HMD pattern with corresponding chest radiograph (D) showing normalization (Group 2)
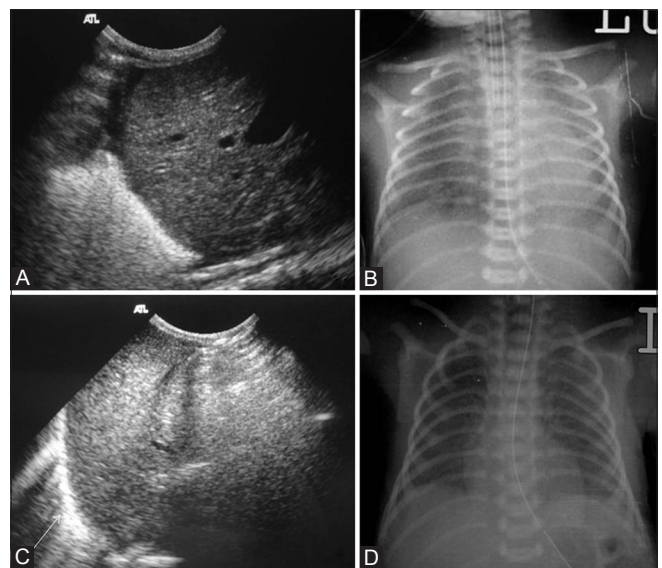

Figure 4 (A-D): A 10-hour-old newborn boy born at 28+3 weeks of gestation having respiratory distress at birth. Coronal TASL (A) shows an HMD pattern. Corresponding chest radiograph (B) taken on day 1 shows low volume lungs with granular opacities and few central air-bronchograms. Coronal TASL (C) at day 11 shows transformation to BPD pattern with corresponding chest radiograph (D) (Group 3). Child was diagnosed as BPD on day 28 of life

Table 3: Comparison of various studies in diagnosis of HMD by TASL

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Avni *et al.*[8]	91.6	100	100	88.8	95
Bober *et al.*[9]	100	92	-	-	-
Present study	84.2	88	84.2	88	86.4

HMD: Hyaline membrane disease, PPV: Positive predictive value, NPV: Negative predictive value, TASL: Transabdominal ultrasound of lung bases

Table 4: Comparison between various studies predicting BPD on TASL

Study	Reference no.	Earliest BPD prediction (in days)
Avni *et al.*	10	18
Pieper *et al.*	11	09
Our study	-	14

BPD: Broncho-pulmonary dysplasia

14 of life [Table 4]. We feel that although highly sensitive, the sonographic BPD pattern is not pathognomonic for eventual development of clinical BPD as this pattern was seen transiently in three HMD patients in our study. It is possible that this transient pattern might have been seen in more patients had the interval of follow-up USG been shorter. However, it cleared in all of them on follow-up. Early prediction of future BPD can help the pediatricians in instituting appropriate interventional strategies like limiting oxygen flow/concentration, using antioxidants, etc., to prevent future complications related to hyperoxygenation. Some authors[14] have shown a transthoracic approach to be better for evaluation and follow-up of HMD.[14] Transthoracic lung USG (TTLS) has the capability to image from anterior, posterior, and lateral positions, and thus evaluates the entire lung as against the transabdominal approach which evaluates only the lung bases. However, it requires more time and patient handling. Copetti, *et al.*[14] have reported the combination of whiteout lung, absence of areas of sparing and pleural line abnormalities to be 100% sensitive and specific for the diagnosis of HMD. Currently there are no studies reported comparing TASL and TTLS. Given the consistently good results for USG of the lungs in the diagnosis and follow-up of HMD, we believe that its use as a routine clinical tool, rather than just a research tool, be explored. One of the major problems in employing it is the delay (12 ± 3 h; 4-20 h in the present study) involved due to the non-availablity of a radiologist. To overcome this delay, we recommend installation of ultrasound machines in NICUs and training of neonatologists in data acquisition. Apart from the clinical aspect, quick documentation of the HMD sonographic pattern is also of medicolegal significance when surfactant administration concerns are present.

Our study has some limitations. Firstly, the sample size of patients who ultimately developed BPD was small (only 6) resulting in our inability to define the exact day of early prediction of BPD with precise significance. Secondly, the ultrasound operator was not blinded to the clinicoradiologic findings of the neonates while performing the sonographic examination. Thirdly, surfactant administration was done in 30/43 patients prior to the ultrasound examination, which might have altered the sonographic appearances.

To summarize, our study supports a complementary role for ultrasound in the diagnosis and follow-up of HMD and for the early prediction of BPD. We recommend (i) future studies exploring the diagnostic utility of ultrasound of lung by neonatologists and comparing their performance with those of radiologists and (ii) prospective studies comparing TASL and TTLS.

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