Original Article

Diagnosis and management of neonatal respiratory distress syndrome in Japan: A national survey

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Key Words
Preterm infants;
Respiratory distress syndrome;
Stable microbubble rating;
Surfactant

Background: Respiratory distress syndrome (RDS) is characterized by a lack of lung surfactant; therefore, biochemical evidence of surfactant deficiency is needed to diagnose RDS. European guidelines recommend surfactant administration when patients need fraction of inspired oxygen exceeding 0.3 on continuous positive airway pressure or intubation. We hypothesized that the European guidelines for surfactant administration were not adopted in Japan because of the lack of RDS diagnosis. This study aimed to investigate neonatologists’ attitudes and practices regarding the diagnosis and management of RDS in Japan.

Methods: A mail-based survey regarding the diagnosis and management of RDS was conducted at 111 level III or IV neonatal intensive care units in Japan. The questionnaire was completed by the person in charge of each unit.

Results: The overall response rate for the questionnaire was 91% (101/111 centers). All respondents referred to chest radiography, and the majority (83%) of respondents referred to stable microbubble rating (SMR) for establishing the diagnosis of RDS. Surfactant administration was chiefly based on clinical conditions, chest radiography, and/or SMR. Most units in Japan do not adopt the European criteria for surfactant administration.

Conclusion: In Japan, chest radiography and/or SMR are commonly used for the diagnosis of RDS and as the rationale for surfactant administration. Further studies from other countries are required to establish the ideal criteria for surfactant administration.

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1. Introduction

Japan has one of the lowest rates of severe neurological injuries and mortality in the world; in particular, the mortality rate of extremely preterm infants is much lower in Japan than in other developed countries. Little is known of the reasons for these good outcomes in Japan, and we speculate that respiratory management after birth may be a contributing factor.

Respiratory distress syndrome (RDS) is one of the most common causes of morbidity and mortality in preterm infants. RDS is characterized by a lack of lung surfactant. Thus, biochemical evidence of surfactant deficiency is needed for its diagnosis. Surfactant should be administered to patients with RDS because endotracheal intubation is associated with hypoxemia, bradycardia, hypertension, and intracranial hemorrhage. Stable microbubble rating (SMR) with gastric aspirates, tracheal aspirates, or amniotic fluid is a rapid, simple, and reproducible test that reflects the adequacy of pulmonary surfactant levels. The test is based on the fact that surfactant stabilizes microbubbles <15 µm in diameter. Briefly, after suctioning and expelling obtained aspirates (approximately 40 µL) on an objective micrometer slide, microbubbles (bubbles < 15 µm in diameter) are counted. The sample is assigned a SMR as follows: >20 stable microbubbles/mm², strong; 10 to 20 stable microbubbles/mm², medium; 2 to 10 stable microbubbles/mm², weak; <2 stable microbubbles/mm², very weak; no stable microbubbles, zero. "Strong" indicates sufficient surfactant and the other ratings indicate deficiencies. Representative images are shown in Fig. 1. The technique is reportedly useful for predicting RDS or failure of continuous positive airway pressure (CPAP) after birth. However, this technique may not be widely used in most neonatal intensive care units (NICUs) worldwide. To date, various changes in surfactant administration have been applied to manage RDS in preterm infants. CPAP is internationally recognized as the first-line therapy for RDS. In addition, the use of a non-invasive approach for surfactant administration (e.g., INSURE: intubation-surfactant-extubation and LISA: less invasive surfactant administration) has also been reported to prevent the development of bronchopulmonary dysplasia (BPD). In Japan, infants are resuscitated according to Japan’s Neonatal Cardio-Pulmonary Resuscitation guidelines which were developed in accordance with the neonatal resuscitation guidelines; CPAP is also the first choice for providing respiratory support when the infants have spontaneous or regular breathing or start to breathe regularly after providing positive pressure ventilation with a bag and mask. However, the INSURE method is not commonly used for preterm infants with less than 28 weeks of gestation because of the risk of intraventricular hemorrhage from unstable respiratory and circulatory dynamics.

European guidelines recommend surfactant administration when patients need fraction of inspired oxygen (FiO₂) exceeding 0.3 on CPAP or intubation. To date, these guidelines have been widely adopted around the world. However, the management of RDS and surfactant administration strategies may differ considerably across centers and countries. For example, a recent national US survey revealed that LISA is not widely used, although the technique is well adopted in Europe. In Japan, it is recommended that surfactant should be administered based on a diagnosis of RDS by combining FiO₂, inspiratory pressure needs, SMR, and chest radiography. A summary comparison of RDS diagnosis and surfactant administration between Japan and Europe is shown in Table 1.

We considered that revealing the management policies of RDS in Japan may be informative to enable further good outcomes in preterm infants. We hypothesized that the European guidelines for surfactant administration have not been adopted in Japan because of the lack of RDS diagnosis. Hence, this study aimed to investigate neonatologists’ attitudes and practices regarding the diagnosis and management of RDS in Japan.

2. Methods

In May and June 2021, a mail-based survey regarding the diagnosis and management of RDS was conducted at 111 level III or IV NICUs in Japan, excluding our unit. The...
Grunting respiration, retraction, tachypnea, and nasal flaring. Diffuse reticulo-granular pattern with air bronchograms. Only 10 units (12%) administered surfactant according to the patients’ gestational age (GA). In 84 NICUs that routinely used SMR to diagnose or manage RDS, all respondents referred to chest radiography, and/or SMR. Some units administered surfactant only based on the result. INSURE was performed in 44 units (44%). Among these 44 units, only seven units (16%) applied the technique in all patients, and most of the respondents applied it according to the patients’ GA; 11 units (25%) applied the technique to patients with GA > 26 weeks, 13 units (30%) to patients with GA > 28 weeks, six units (14%) to patients with GA > 30 weeks, and two units (5%) to patients with GA > 32 weeks. LISA was performed in only one unit. Lung ultrasound was performed in only four units (4%) for the diagnosis or management of RDS (Table 2).

Most NICUs in Japan did not adopt the European criteria for surfactant administration or accept these criteria. The reasons for this are shown in Table 2.

5. Discussion

This national survey revealed neonatologists’ attitudes and practices regarding the diagnosis and management of RDS in Japan. We found that most Japanese neonatologists administered surfactants based on the diagnosis of RDS instead of merely FiO2 as recommended by the European guidelines. Moreover, most NICUs do not adopt the European guidelines for surfactant administration.

Since RDS is associated with a lack of lung surfactant, evidence of surfactant deficiency is needed for an accurate diagnosis.5 Our study revealed that, in Japan, chest radiography and/or SMR are commonly used for the diagnosis of RDS and as the rationale for surfactant administration. SMR can detect the prematurity of the lung surfactant system and is considered a useful tool for predicting RDS.9 This technique is a simple and quick biological surfactant test that requires only a few minutes; however, intra- and inter-observer variability may influence the results.10 Moreover, sample contamination also influences the result, for example, when infants aspirate bloody amniotic fluid or meconium during labor, the results of SMR appear “weak” because these contaminations inactivate the surfactant.19,20 In our survey, only 10 units (12%) administered surfactant only based on SMR, and the majority administered surfactant by combining SMR, chest radiography, and clinical conditions. Although SMR is a useful tool to derive evidence of surfactant sufficiency or deficiency, the results should be interpreted cautiously also considering the clinical conditions, need for FiO2, and chest radiography.
Table 2  Questionnaire and responses on the diagnosis of and management of RDS.

<table>
<thead>
<tr>
<th>Questionnaire on the diagnosis of RDS</th>
<th>Number (%) of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 101</td>
</tr>
<tr>
<td>Have you experienced confusion when diagnosing of RDS?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (78)</td>
</tr>
<tr>
<td>No</td>
<td>22 (22)</td>
</tr>
<tr>
<td>What do you refer for establishing the diagnosis of RDS? (multiple answers allowed)</td>
<td></td>
</tr>
<tr>
<td>SMR with gastric aspirates</td>
<td>81 (80)</td>
</tr>
<tr>
<td>SMR with amniotic fluid</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>101 (100)</td>
</tr>
<tr>
<td>Clinical conditions</td>
<td>73 (72)</td>
</tr>
<tr>
<td>Effect of surfactant</td>
<td>69 (68)</td>
</tr>
<tr>
<td>Need of FiO2</td>
<td>64 (63)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionnaire on the management of RDS</th>
<th>Number (%) of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 101</td>
</tr>
<tr>
<td>What are your criteria for the administration of surfactant? (multiple answers allowed)</td>
<td></td>
</tr>
<tr>
<td>RDS diagnosis based on clinical conditions</td>
<td>92 (91)</td>
</tr>
<tr>
<td>RDS diagnosis based on SMR and/or chest radiography</td>
<td>82 (81)</td>
</tr>
<tr>
<td>Need for FiO2 exceeding 0.3 on CPAP</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Need for intubation</td>
<td>12 (12)</td>
</tr>
<tr>
<td>All patients with GA &lt; 27 weeks</td>
<td>8 (8)</td>
</tr>
<tr>
<td>All patients with GA &lt; 26 weeks</td>
<td>7 (7)</td>
</tr>
<tr>
<td>All patients with GA &lt; 25 weeks</td>
<td>3 (3)</td>
</tr>
<tr>
<td>All patients with GA &lt; 24 weeks</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All patients with GA &lt; 23 weeks</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Do you administer surfactant only based on SMR? (N = 84)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (12)</td>
</tr>
<tr>
<td>No</td>
<td>74 (88)</td>
</tr>
<tr>
<td>Do you use INSURE in patients with adequate spontaneous breathing?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (44)</td>
</tr>
<tr>
<td>No</td>
<td>57 (56)</td>
</tr>
<tr>
<td>What are your application policies for INSURE? (N = 44)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>7 (16)</td>
</tr>
<tr>
<td>All patients with GA &gt; 32 weeks</td>
<td>2 (5)</td>
</tr>
<tr>
<td>All patients with GA &gt; 30 weeks</td>
<td>6 (14)</td>
</tr>
<tr>
<td>All patients with GA &gt; 28 weeks</td>
<td>13 (30)</td>
</tr>
<tr>
<td>All patients with GA &gt; 26 weeks</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Non-specific policies</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Do you use LISA in patients with adequate spontaneous breathing?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1)</td>
</tr>
<tr>
<td>No</td>
<td>100 (99)</td>
</tr>
<tr>
<td>Do you use lung ultrasound for the management of daily respiratory care?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (8)</td>
</tr>
<tr>
<td>No</td>
<td>93 (92)</td>
</tr>
<tr>
<td>Do you use lung ultrasound for the diagnosis or management of RDS?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (4)</td>
</tr>
<tr>
<td>No</td>
<td>97 (96)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionnaire on the adoption of the European criteria for surfactant administration</th>
<th>Number (%) of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 101</td>
</tr>
<tr>
<td>Does your unit use the European criteria for the surfactant administration?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (6)</td>
</tr>
<tr>
<td>No</td>
<td>95 (94)</td>
</tr>
<tr>
<td>Do you agree with the European criteria for the surfactant administration?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (15)</td>
</tr>
<tr>
<td>No</td>
<td>79 (78)</td>
</tr>
<tr>
<td>No response</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>
The differences in the surfactant administration protocols between Japan and Europe may result from their different respiratory management policies. Presently, for the management of preterm infants, avoiding mechanical ventilation is important for preventing the development of BPD, and the first-line therapy for the management of RDS is CPAP. However, in Japan, it is recommended that preterm infants, especially those with <25 weeks of gestation, should be placed on mechanical ventilation for at least 72 h after birth to stabilize their circulatory and respiratory statuses. Cardiac dysfunction due to an increased afterload is associated with intraventricular hemorrhage. These may be the key reasons for the lower adoption of INSURE and LISA in Japan, especially LISA. Attitudes regarding LISA are the same as in the US where only 10% of American neonatologists accept the evidence of LISA as recommended standard care. Although the incidence of BPD is high in Japan, such a respiratory management policy leads to the lowest rates of severe neurological injuries and mortality.

The European guidelines for surfactant administration were not commonly adopted in Japan, and most Japanese neonatologists did not agree with them. The main reason was that oxygenation dependency with CPAP does not only result from surfactant deficiency. Subsequently, lack of evidence of surfactant deficiency or RDS diagnosis was noted. The PEEP level influences the threshold of FiO₂. In fact, the threshold of 0.3 FiO₂ was based on a single-center, retrospective study. The American Academy of Pediatrics does not recommend any threshold of FiO₂ for surfactant administration. Thus, the threshold of FiO₂ is not appropriate for reflecting lung biology in patients with RDS, and it could lead to unnecessary treatment, causing airway obstruction, bradycardia, desaturation, and economic burden. Moreover, surfactant administration requires tracheal intubation, which is associated with risk of intraventricular hemorrhage. In fact, the incidence of intraventricular hemorrhage in Japan is much lower than those in other developed countries. We believe that surfactant administration based on an RDS diagnosis is suitable for feasible care in preterm infants.

In Japan, there are concerns regarding the management of RDS. First, clinicians are often confused when establishing the diagnosis of RDS. Although transient tachypnea of the newborn (TTN) is due to delayed clearance of lung fluid, this syndrome also results from mild immaturity of the lung, and surfactant administration may be effective. Thus, the differential diagnosis between RDS and TTN is sometimes difficult. In such cases, surfactant administration based on the respiratory status may be reasonable without establishing a diagnosis. Second, the use of chest radiography or SMR often takes time and leads to delay in treatment. Surfactants should be administered as early as possible. Recently, lung ultrasound has been used for determining surfactant administration. Lung ultrasound is non-invasive, repeatable, and provides real-time information at the bedside. Moreover, lung ultrasound-guided surfactant administration is a useful tool for early surfactant administration. However, the use of lung ultrasound is very low in Japan. Further application of the technique is expected for early surfactant administration, leading to better respiratory outcomes in Japan.

Our study has some limitations. Although the response rate of our survey was excellent, the survey was only conducted at 111 level III or IV NICUs and was not conducted at 296 level II NICUs in Japan. Moreover, the questionnaire

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**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Questionnaire on the diagnosis of RDS</th>
<th>Number (%) of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why do you disagree with the European criteria? (N = 79) (multiple answers allowed)</td>
<td>N = 101</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant should be administered based on the evidence of surfactant deficiency</td>
<td>38 (48)</td>
</tr>
<tr>
<td>Oxygenation dependency with CPAP results from not only surfactant deficiency</td>
<td>65 (82)</td>
</tr>
<tr>
<td>Lack of differential diagnosis with other oxygen-dependent lung diseases</td>
<td>43 (54)</td>
</tr>
<tr>
<td>FiO₂ threshold does not represent RDS pathology</td>
<td>42 (53)</td>
</tr>
<tr>
<td>PEEP level is unclear</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Definition of intubation is unclear</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Chest radiography, SMR, and clinical conditions should be referred to</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Respiratory failure improves in some patients after intubation without surfactant administration</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Respiratory failure improves in some patients with CPAP and FiO₂ 0.3</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Surfactant administration and intubation are not equivalent</td>
<td>2 (3)</td>
</tr>
<tr>
<td>No response</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; GA, gestational age; INSURE, intubation-surfactant-extubation; LISA, less invasive surfactant administration; PEEP, positive end-expiratory pressure; RDS, respiratory distress syndrome; SMR, stable microbubble rating.
was completed by the chief of each unit and may not have reflected the consensus of all within the unit. Thus, our study does not completely describe neonotologists’ general attitudes and practices regarding the diagnosis and management of RDS in Japan. In addition, we did not survey the relationships between the policies of diagnosis of RDS or surfactant administration and neurological outcomes.

6. Conclusion

In Japan, chest radiography and/or SMR are commonly used for the diagnosis of RDS and as the rationale for surfactant administration. Surfactant administration based on an RDS diagnosis appears suitable for feasible care in preterm infants. Further studies from other countries are required to establish the ideal criteria for surfactant administration.

Disclosure

The abstract was submitted to the 58th Annual Meeting of the Japan Society of Perinatal and Neonatal Medicine held in Yokohama, from July 10 to 12, 2022.

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Declaration of competing interest

The authors declare no conflict of interest relevant to this article.

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References


Appendix A. Supplementary data

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