Role of Lung Ultrasonography to Evaluate Surfactant Need in Preterm Neonates in Suez Canal District

Protocol of Thesis Submitted in Partial Fulfillment of MD Degree in Pediatrics and Neonatology

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INTRODUCTION AND RATIONALE

Respiratory distress syndrome (RDS) continues to represent a crucial problem for preterm neonates despite the new advancement in its management over the last years which leads to improved survival for extreme preterm neonates but with increased incidence of bronchopulmonary dysplasia (Stoll et al. 2015).

Overall, incidence of RDS is affected by gestational age; occurring in about 45% of early and moderate preterm neonates (24-33 weeks), reduced to 4% in late preterm neonates (34-36 weeks) and less than 1% in full term neonates (Condò et al. 2017).

Ratio of neonatal intensive care unit (NICU) admission by RDS as a part of total NICU admission is increasing yearly with the highest increase in RDS incidence in extreme preterm neonates. Many risk factors contribute to this increase such as old maternal age, planned caesarean sections and increased incidence of premature delivery especially after in vitro fertilization and other assistive reproductive techniques (Sun et al. 2013; Frangez et al. 2014; Martin et al. 2018).

Management of preterm neonates with RDS should be started even before their birth, prenatal corticosteroids given to mother with expected premature delivery improve survival and reduce risk of RDS, necrotizing enterocolitis (NEC) and intraventricular hemorrhage (Roberts et al. 2017), also extremely preterm neonates should be born in centers with tertiary NICU to receive their initial neonatal care with better long term outcomes (Rautava et al. 2013).

Currently, using early continuous positive airway pressure (CPAP) in the management of preterm neonates since birth together with early selective administration of surfactant, for those with signs of ongoing RDS, is an alternative to prophylactic surfactant administration (Papile et al. 2014). On the other hand, surfactant prophylaxis is no longer indicated for preterm neonates stabilized by non-invasive respiratory support (Sweet et al. 2017).

Early selective surfactant administration for preterm neonates with signs of RDS is very important, it improves the outcome and decrease risk for air leak syndromes, neonatal mortality and chronic lung diseases compared to delayed administration after worsening of RDS (Bahadue
New methods in diagnosis for assessment of endogenous surfactant and lung maturity as lamellar bodies count present in gastric aspirate are now available to help in detecting preterm neonates need early surfactant administration (Verder et al. 2013). However these methods can’t be widely adopted because of technical difficulties, and there is an increasing needs for a simple bedside test that can be done within the NICU (Sweet et al. 2017). LUS may be a helpful tool (Sweet et al. 2019).

Lung ultrasound (LUS), as a simple and non-invasive diagnostic technique with no exposure to ionizing radiation, can be used as a reliable diagnostic tool for causes of neonatal respiratory distress with good sensitivity and specificity, as reported in a literature review (Sharma and Farahbakhsh 2019). It can be used not only for early diagnosis of transient tachypnea of newborn (TTN) but also Lung ultrasound score can be used for predicting the clinical course of the disease and monitoring lung aeration (Ibrahim et al. 2018; Raimondi et al. 2019). Another uses for LUS includes diagnosis of congenital diaphragmatic hernia, if prenatal diagnosis is missed, and diagnosis of pulmonary hemorrhage of newborn (Ren et al. 2017; Corsini et al. 2019).

LUS can be used in diagnosis of RDS with high sensitivity and specificity, as reported in a literature review, about 97% and 91% respectively (Hiles et al. 2017). Concurrent detection of lung consolidation, abnormalities of pleural line and either bilateral white lung or A-line disappearance can diagnose RDS with sensitivity and specificity of 100% (Liu et al. 2015). It can also predict the need for surfactant (Gregorio-Hernández et al. 2020; Perri et al. 2020; Razak and Faden 2020).

LUS can be used in diagnosis of RDS complication with better detection, compared to Chest X-ray, of consolidation and sub-pleural atelectasis (Lovrenski et al. 2015; Sawires et al. 2015; Ibrahim et al. 2018). It can be used also in follow up and early assessment of the response to surfactant replacement therapy (El-Malah et al. 2015; Lovrenski et al. 2015).

In this study we will assess the applicability of lung ultrasonography to evaluate the surfactant need in preterm neonates ≤ 34 weeks treated with early CPAP according to European
guidelines 2016 update. We will also assess response to surfactant replacement therapy and need for second dose of surfactant.

**AIM OF THE WORK**

Finding simple, available and non-invasive diagnostic modality to help in deciding whom to treat with surfactant replacement therapy.

**STUDY OBJECTIVES**

**Primary Objectives**

- Assess the applicability of lung ultrasonography for early prediction of the surfactant need in preterm neonates ≤ 34 weeks treated with CPAP.

**Secondary Objectives**

- Assess the response to early selective replacement therapy in premature neonates using lung ultrasonography.
- Predict need for second dose of surfactant replacement therapy using lung ultrasonography.

**RESEARCH QUESTIONS**

Can lung ultrasonography predict need for surfactant replacement therapy in preterm neonates ≤ 34 weeks treated with CPAP?

**HYPOTHESIS**
Lung ultrasonography can predict need for surfactant replacement therapy in preterm neonates ≤ 34 weeks treated with CPAP

SUBJECTS AND METHODS

Study design:

Cross sectional analytic study

Target population:

Premature neonates ≤34 week admitted to neonatal intensive care unit (NICU) and treated on positive continuous airway pressure (CPAP).

Study population:

Study population will be sampled from premature neonates ≤34 week admitted to neonatal intensive care unit (NICU) in Suez Canal University hospital, AL Salam Portsaid hospital and Port Said Specialized Obstetrics and Gynecology hospital.

Preterm neonates (≤ 34 weeks) admitted to NICU and met the inclusion criteria will be enrolled in the study.

Inclusion criteria:

Preterm neonates (≤ 34 weeks) admitted to NICU treated by CPAP according to European guidelines 2019 update.

Exclusion criteria:

1. Chromosomal aberrations or complex congenital malformations
2. Congenital lung diseases
3. Congenital pneumonia
4. Severe neonatal sepsis and septic shock
5. Meconium aspiration syndrome
6. Surfactant administration in delivery room as per European guidelines 2019 update

(Sweet et al. 2019).

**Sample type:**

Convenience sampling. Neonates admitted to the NICU eligible for the study's criteria between September 2020 and September 2021 will be chosen.

**Sample size:**

Sample size was calculated using MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2018), setting the type-1 error (α) at 0.05 and the power (1-β) at 0.95. Results from a previous study (Brat et al. 2015) showed that the ROC analysis for LUS score in the prediction of the need for surfactant in neonates had an area under the curve (AUC) of 0.83, with 20% of preterm neonates under study receiving surfactant. Based on these values the calculated sample size is 55 neonates only, with a drop out of about 10% of the cases. The total sample size will be **60 neonates**.
**Methods:**

In details, according to European guidelines 2019 update, preterm neonates who doesn’t respond to bag& mask ventilation and require intubation will receive surfactant in the delivery room and be excluded from the study. Spontaneously breathing preterm neonates will be stabilized with early NCPAP of 6 cm H₂O. LUS will be done in the first 2 hours of life. Surfactant will be administered whenever fraction of inspired oxygen (Fio₂) requirements exceeds 0.30 through INSURE technique [intubate-surfactant-extubate] (Sweet *et al.* 2019).

A high resolution linear transducer with a frequency of 3-12 MHz will be used in this study. The images will be obtained using Philips CX50 ultrasound scanner. LUS will be performed by a single performer (neonatologist trained on neonatal LUS and had 3 months of hands on experience under supervision before the study) within the first 2 hours of admission before surfactant administration. While in a quiet state, neonates are positioned in a supine, side and prone position, each lung will be divided into 6 areas (upper anterior, lower anterior, upper lateral, lower lateral, upper posterior and lower posterior) and examined using a linear transducer through both transverse and longitudinal scans. 0 to 3 point score will be given for each lung area (total score ranging from 0-36 in both lungs).

The result of lung ultrasound will be masked to clinicians who will decide whether to use surfactant or not and the LUS performer will not be involved in decision-making in treating the preterm neonates. In the neonates who will receive surfactant replacement therapy, another LUS assessment will be done within 2 hours after surfactant administration.

The LUS score will be modified from a score proposed for adult patients (Via *et al.* 2012). It was used in a previous study on neonates to evaluate oxygenation and surfactant need, it includes the full spectrum of possible conditions; normal lung aeration, interstitial pattern, alveolar pattern and consolidation (Brat *et al.* 2015).
In details, LUS is designed as follows:

- 0 score for A-pattern (indicates presence of A lines only).
- 1 score for B-pattern (indicates presence of $\geq 3$ well-spaced B-lines).
- 2 score for severe B-pattern (indicates presence of crowded and coalesced B-lines with or without subpleural consolidations).
- 3 score for extended consolidations.

Detailed medical history will be taken and detailed physical examination will be performed. Also basic laboratory tests and chest x-ray findings will be obtained from medical records for each case if indicated.

The data will be recorded in a case sheet, the case sheet is divided into five sections: personal data, perinatal data, clinical data, laboratory data and radiological data including chest x-ray and lung ultrasonography.

Personal data encompasses name, sex, age, gestational age and weight on delivery. Perinatal history includes questions for analysis of specific risk factors. Clinical data gives an idea about the oxygen needs and general assessment of respiratory, cardiac and abdominal systems. Laboratory data consists of the basic investigations performed. Radiological data shows the findings either in plain Chest x-ray antero-posterior view or in LUS examination. The case sheet is included in the appendix section.

**DATA COLLECTION**

Data will be collected from the previously mentioned study population after setting the inclusion and exclusion criteria. LUS will be performed. The data obtained will be recorded in the case sheet.
STATISTICAL ANALYSIS

Statistical analysis will be done by Statistical Package for Social Science (SPSS) for windows version 21.

ETHICAL CONSIDERATION

1. Administrative permissions will be requested from the hospitals in which the study will be performed.
2. Participant’s family will be informed with the aim of the study and its benefit to their neonate.
3. Ensuring the confidentiality of data collected, and that no data are going to be used outside this study without personal approval.
4. Informed consent will be obtained from the parents.
5. No invasive maneuver will be performed or used.
6. Ensuring that performing the test will not interrupt the plan of management.
7. The researcher’s phone number will be provided to the parents for any enquiries.
8. The family has the right to withdraw from the research at any time or even refuse to participate from the beginning with no effect on the decisions taken for the plan of the management.
TIME TABLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration/Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory phase</td>
<td>3 months</td>
</tr>
<tr>
<td>Data collection</td>
<td>12 months</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>1 month</td>
</tr>
<tr>
<td>Computer writing</td>
<td>2 months</td>
</tr>
<tr>
<td>Data preparation for presentation</td>
<td>1 month</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Twenty Months</strong></td>
</tr>
<tr>
<td>Data Collection</td>
<td>3000 LE</td>
</tr>
<tr>
<td>Data Management</td>
<td>2000 LE</td>
</tr>
<tr>
<td>Preparation of final book and presentation</td>
<td>3000 LE</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8000 LE</strong></td>
</tr>
</tbody>
</table>

References


**Appendix**

**Case Sheet**

**Personal data:**
Name: 
Sex: 

Gestational Age: 
Weight on Delivery: 

**Peri-Natal History:**

**Suggestive of RDS**

| History of Diabetes Mellitus: | -Yes | -No |
| Mode of Delivery: | -C.S | -VD |
| If C.S | -Elective | -Labor pain |
| Type of anesthesia: | -Genera | -Local |

| History of Peri-natal asphyxia: | -Yes | -No |

| Number of delivered babies: | -Single | -Multiple |

| History of perinatal steroids: | -Yes | -No |

| History of prolonged intrauterine stress | - Yes | -No |

**Suggestive of other pathology**

| History suggestive of maternal TORCH infection: | -Yes | -No |

| History of PROM: | -Yes | -No |
| If Yes | -<18hrs | ->18hrs |

| History of UTI during pregnancy: | -Yes | -No |

| Color of amniotic fluid: | -Clear | -Meconium |

**Clinical Data:**

| Main Complaint: | -RD | -Else |
| If RD What grade? | -I | -II | -III | -IV |

| The patient is on Oxygen support? | -Yes | -No |
| If Yes What type? | -Nasal | -nCPAP | -Invasive CPAP | -MV |

| Chest Examination Findings: | -Fine Crepitations (-Unilateral -Bilateral) |
| -Coarse Crepitations (-Unilateral -Bilateral) |
| -Diminished air entry(-Unilateral -Bilateral) |
| -No abnormality detected |
Cardiac Examination Findings:
- Murmur (-Systolic -Diastolic)
- Accentuated Heart sounds (-S1 – S2 -Both)
- NAD

Abdominal Examination Findings:
- Organomegaly (-Liver – Spleen -Other)
- Marked Abdominal Distension (-Yes -No)
- NAD

Laboratory Data: (medical records)

HB (The patient is anemic?)
- Yes
  If Yes What Degree?
  - Mild
  - Moderate
  - Severe
- No

TLC
- Leukocytosis
- Leucopenia
- Normal

Platelets
- Thrombocytopenia
- Thrombocytosis
- Normal

CRP
- Elevated
- Normal

ABG
- Respiratory Acidosis (-Compensated -Uncompensated)
- Metabolic Acidosis (-Compensated -Uncompensated)
- Respiratory Alkalosis (-Compensated -Uncompensated)
- Metabolic Alkalosis (-Compensated -Uncompensated)
- Normal

Cultures (If Done):
- Blood
  If Positive What is the organism?
  (-Positive
  - Negative)
- Sputum
  If Positive What is the organism?
  (-Positive
  - Negative)
- C.S.F
  If Positive What is the organism?
  (-Positive
  - Negative)
Radiological Data:

CXR Findings: (medical records)

<table>
<thead>
<tr>
<th>Suggestive of RDS</th>
<th>Suggestive of Other Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass appearance</td>
<td>Pneumonic Patch</td>
</tr>
<tr>
<td>Air bronchogram</td>
<td>Lobe Collapse</td>
</tr>
<tr>
<td>White lung</td>
<td>Pleural Effusion</td>
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<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Cardiomegaly</td>
</tr>
<tr>
<td></td>
<td>Emphysematous changes</td>
</tr>
</tbody>
</table>

Chest Ultrasonography Findings:

<table>
<thead>
<tr>
<th>Finding</th>
<th>Lung areas</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-pattern: A lines only</td>
<td></td>
<td></td>
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<tr>
<td>B-pattern: $\geq3$ well-spaced B lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe B-pattern: crowded and coalesced B-lines with or without subpleural consolidations</td>
<td></td>
<td></td>
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<tr>
<td>Extensive consolidation</td>
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<tr>
<td>Total score</td>
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الملخص العربي

مقدمة:

تعتبر متلازمة صعوبة التنفس من أهم المشاكل الصحية التي تواجه الأطفال المبتسررين وذلك بالرغم من التقدم الحادث في طرق علاجها في السنوات الأخيرة والتي أدت إلى تحسن معدل الشفاء, وتأثر معدلات حدوثها بالعمر الجنيني للطفل فتزداد نسبة حدوثها كلما قل العمر الجنيني.

وتزداد سنويا نسبة حجز الأطفال بوحدة الحضانات بمتلازمة صعوبة التنفس نتيجة عوامل متعددة منها أكبر عمر الأمهات، زيادة معدلات الولادات القيصرية المرتب لها و زيادة معدلات ولادة المبتسررين خاصة بعد أطفال الأنابيب وغيرها من الوسائل المساعدة.

ويبدأ التعامل مع المبتسررين المصابين بمتلازمة صعوبة التنفس حتى من قبل ولادتهم عن طريق اعطاء الأمهات المتوقعة ان تلد مبكراً السترويدات أثناء الحمل ونقلهم إلى المستشفيات التي تتوفر بها حضانات مجهزة لتقديم رعاية طبية فائقة.

ويصبح في هذه الأيام باستخدام الضغط الهوائي الإيجابي المستمر في علاج الأطفال المبتسررين منذ ولادتهم مع استخدام مخفضات التوتر السطحي مبكراً في الحالات التي يظهر عليها أعراض متلازمة صعوبة التنفس، وبحسن الحقن المبكر لمخفضات التوتر السطحي من نتائج الحالات كما يخفض معدلات الوفيات والمضاعفات طويلة الأمد. ومع ذلك ليس هناك دليل على أن الحقن الاستباقي لمخفضات التوتر السطحي للأطفال المبتسررين إما كانت أعمارهم الجنينية أفضل من استخدام الضغط الهوائي الإيجابي المستمر مبكراً.

وما أوجد حاجة ماسة لتقديم أكتمال نمو الرئة وتكوين مخفضات التوتر السطحي الطبيعية عن طريق أساليب تشخيصية جديدة مثل عدد الأجسام الرفقتية في عصارة المعدة، ولكن مثل هذه الطرق لا يمكن استخدامها على نطاق واسع لصعوبات تقنية.

وعتبر الالعاب الصوتية طريقة تشخيصية سهلة لا تشمل التعرض للأشعة بحساسية تشخيصية مرتفعة تصل إلى 97% كما أنه يمكن استخدامها لتشخيص المضاعفات المتوقعة وكذلك استجابة الحالات للعلاج بمخفضات التوتر السطحي وهذا ما سيتم تقييمه في هذه الدراسة.
الغرض من الرسالة:

في هذه الرسالة سيتم تقييم إمكانية استخدام الموجات الصوتية للتنقيم المبكر لاحتياج العلاج بمجموعة من الأطفال السطح في الأطفال المبتسرين و 34 أسبوع والذين يتم علاجهم بالضغط الهوائي الإيجابي المستمر.

تصميم الرسالة:

هذه الرسالة تحليلية مستقطعة والتي ستقام على الأطفال المبتسرين و 34 أسبوع والذين يتم حجزهم بحضانة مستشفيات جامعة قناة السويس مستشفى النساء والولادة التخصصي ببورسعيد.

طريقة أخذ العينات:

سيتم أخذ العينات بطريقة أخذ العينات العشوائية البسيطة، وتتمثل العينة المطلوبة في عدد 60 طفل مبستر و 34 أسبوع.

طريقة الحصول على المعلومات:

سيتم عمل موجات صوتية على الرئة لجميع الحالات في خلال ساعتين من الولادة وسيتم تقييم كل حالة بمجموع نقاط من صفر إلى 36، وسيتم علاج الحالات طبقًا لقواعد الإرشادية الأوروبية 2016 وسيتم حجب نتيجة الموجات الصوتية عن الطبيب المعالج حتى لا تؤثر على قرار الاحتياج إلى موجات التوتر السطحي عن عدمه، وسيتم تسجيل هذه الانتباذية باستمارة للمريض بالإضافة إلى بيانات المريض الأخرى التي تحتوي على تاريخه الطبي وفحصه الاكليتيكي ونتائج الفحوصات العملية الأخرى ونتائج الاشعة السينية.
دور الموجات فوق الصوتية للرنة لتقديم الاكتشاف لمخاطر التوتر السطحي في حديثي الولادة المبتسرين في منطقة قناة السويس

خطة بحثية للحصول على درجة الدكتوراه في طب الأطفال وحديثي الولادة

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2020