Protocol of a Thesis For Partial Fulfilment of MD Degree in Pediatrics

Title:

Haemodynamic changes with different Noninvasive respiratory modes for primary Respiratory Support in Preterm Neonates

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What is already known on this subject? AND What does this study add?

The use of Noninvasive Respiratory Support (NRS) as primary and post extubation respiratory support in Neonatal Intensive Care Unit (NICU) has increased in recent decades as a means to reduce ventilator-induced lung injury ***(Mukerji and Dunn, 2016).***

The study evaluates the efficacy of Noninvasive High-Frequency Oscillatory Ventilation (NHFOV) and High Velocity Nasal Insufflation (Hi-VNI Vapotherm) in comparison to nasal CPAP as a primary noninvasive respiratory support in preterm infants. It also assesses echographic, cerebral blood flow and mesenteric blood flow changes during NHFOV and Hi-VNI Vapotherm in comparison to nasal CPAP.

1. INTRODUCTION

Respiratory distress is one of the most common causes of admission to NICU. Noninvasive ventilation (NIV) has significantly and positively altered the treatment outcomes and improved mortality rates of preterm infants with Respiratory Distress Syndrome (RDS) ***(Permal et al., 2019).***

NIV can reduce the adverse effects associated with intubation and mechanical ventilation, such as bronchopulmonary dysplasia(BPD), sepsis, and trauma to the upper airways. In the last 4 decades, nasal CPAP has been used to wean preterm infants off mechanical ventilation and as a primary mode of respiratory support for preterm infants with respiratory insufficiency ***(Mahmoud et al., 2011).***

Noninvasive high-frequency oscillatory ventilation (NHFOV) is a method of augmenting CPAP support in preterm infants, potentially combining the advantages of both invasive high-frequency oscillatory ventilation and CPAP ***(De Luca and Dell'Orto, 2016).***

Vapotherm 2000i® is a noninvasive high-flow respiratory support system used mainly in the treatment of type 1 respiratory failure. It uses a mixture of oxygen and air to deliver a set concentration via nasal cannula. The advantage of this system is the high humidity achieved using the integral heated water system. The system has been used in neonatal practice as a replacement for nasal CPAP ***(Price et al., 2008).***

Poor aeration of the lung leads to increased pulmonary vascular resistance and reduced blood flow. In contrast, overinflation of the lung causes compression of the vena cava, pulmonary vasculature, and heart. Low systemic blood flow and low superior vena cava (SVC) return are associated with increased morbidity in preterm infants. Therefore, the interaction between respiratory support and cardiac output (CO) is critically important ***(Beker et al.,2014).***

2. AIM/ OBJECTIVES

1. Primary aim is to evaluate the efficacy of NHFOV and Hi-VNI Vapotherm in comparison to nasal CPAP as a primary noninvasive respiratory support in preterm neonates through assessment of:
    - The need for invasive mechanical ventilation (IMV) during the first 72 hours after enrollment in one of the groups, days of hospitalization, days on noninvasive respiratory support, days on supplemental oxygen, mortality, severe retinopathy of prematurity(ROP), air leak syndromes, intraventricular hemorrhage(IVH), necrotizing enterocolitis(NEC), nasal trauma and BPD.
2. Secondary aim is to assess haemodynamic changes during periods of non-invasive respiratory support including echocardiographic, cerebral blood flow and mesenteric blood flow changes.

3. METHODOLOGY:

1. **Type of Study:** Randomized controlled trial.
2. **Study Setting:** NICU of Ain Shams University. Children hospital, Cairo, Egypt.
3. **Study Period:** Two years , from September 2021 till September 2023.
4. **Study Population:** Preterm neonates with RDS requiring noninvasive ventilation, the involved study group will be of matched gestational, postnatal age and sex.
5. **Inclusion Criteria:**

- Preterm neonates with gestational age ≤ 35 weeks with RDS that need noninvasive ventilatory support primarily.

6. Diagnosis of RDS is by clinical presentation, including signs of respiratory distress, ABGs showing hypoxemia and hypercapnia and chest x-ray showing diffuse atelectasis classically described as having a ground-glass appearance . ***(Hermansen and Mahajan ,2015).***
7. The need for noninvasive ventilation in the following situations :

- Preterm with mild to moderate respiratory distress, Silverman score <6 ***(Silverman and Anderson,1956).***
- Mild to moderate hypoxemia (Fio2 less than 50% to maintain SpO2 (90%-94%)
- Mild to moderate respiratory acidosis (PaCO2<65mmHg with pH>7.20)
- Apnea (not associated with bradycardia, not needing bag and mask ventilation)

8. **Exclusion Criteria:**
    1. Patients with major upper or lower airway anomalies.
    2. Patients with significant congenital anomalies including cardiac, abdominal or respiratory.
9. **Sample size:** 90 participants
10. **Sample size calculation:**

Sample size was calculated using One-way ANOVA F-test with significance level 0.05. Calculation according results from a previous study **(*Abdelhady et al.,2008)*** produced a sample size of 30 cases in each group.

11. **Sampling Method:**

Preterms will be allocated randomly to one of 3 groups :

- Group A: it will include 30 preterm neonates on NHFOV

- Group B: it will include 30 preterm neonates on Hi-VNI Vapotherm.
- Group C: it will include30 preterm neonates on nasal CPAP

12.Study Procedures:

1. Detailed antenatal, natal and postnatal history. Gestational age will be estimated using the date of the last menstrual period and confirmed by the new Ballard scoring system ***(Ballard et al., 1991).***
2. Full clinical examination including: chest, cardiac, abdominal , neurological examination and anthropometric measurements.
3. Patients' ages, mean arterial blood pressure, urinary output, temperature , capillary refilling time and O_2 saturation by pulse oximetry and according, Oxygen Saturation Index (OSI) will be calculated as a noninvasive predictor of respiratory failure ***(Muniraman et al., 2019).***
4. Daily inspection of infants' nostrils to evaluate the presence of skin alterations, nasal injury score will be used ***(Khan et al., 2017).***
5. Surfactant if given with recording its timing and doses, Curosurf®; Chiesa pharmaceuticals, Parma, Italy. At a dose of 200 mg/kg will be administered via the INSURE method if an infant present with the following:
   - ≤30 weeks GA when FiO_2 requirement >0.30 or >30 weeks GA when FiO_2 requirement >0.40. In the INSURE technique, surfactant is administered via an endotracheal tube and after a brief period of positive pressure ventilation, patients will be extubated to the assigned mode. ***(Zhu et al., 2018).***
6. Caffeine citrate; Chiesi Pharmaceuticals, Parma, Italy. Will be administered when infants present with significant apnea (defined as three or more episodes in 24 hrs or a single episode requiring resuscitation and bag and mask ventilation). The initial loading dose is 20 mg/kg, and the maintenance dose is 5 mg/kg per day ***(Zhu et al., 2018).***
7. Assessment of feeding; method (parenteral or enteral) and detecting the type of milk, volume and duration to reach full enteral feeding together with recording presence of any feeding intolerance.
8. Recording of patients' days of hospitalization, days on noninvasive respiratory support, days on supplemental oxygen, initial settings and modifications, inotropic support, sepsis, incidence of ROP, air leak syndromes, IVH, NEC, BPD ***(Jobe and Bancalari, 2001)*** and mortality.

Candidates will be randomized into one of 3 groups :

A. NHFOV group: NHFOV will be delivered by; SLE 6000 device, Wipro GE Healthcare Private Limited, Bengaluru, Karnataka. Amplitude range (20:35), frequency range (8-12)HZ, MAP range (6: 10) cmH2O and I:E ratio 1:1 may change to 1:2 in case of air trapping .

B. Hi-VNI Vapotherm group:

Hi-VNI Vapotherm will be delivered by; Vapotherm device,Vapotherm,INC,USA. The recommended starting flow rate is 4-6 L/min. To be titrated to clinical effect to maximum of 8 L/min as needed,with temperature 36-37°C and FiO2 titrated as needed to achieve target SpO2(90% to 94%) ***(Yoder et al.,2017).***

C. Standard noninvasive mechanical ventilation group (CPAP):

CPAP will be delivered by; MEDIN CNO device, medin Medical Innovations GmbH, Olching, Germany . Pressure ranging from 5 to 8 cm H_2O,to maintain target oxygen saturation (SpO_2) from 90% to 94%.

We will define failure of non-invasive mode and need for invasive mechanical ventilation according to the following while on the maximum noninvasive settings :

- Severe respiratory acidosis (PaCO2 ≥ 65 mmHg with pH ≤ 7.20),
- Severe apnea and bradycardia (defined as recurrent apnea with >3 episodes per hour associated with heart rate <100/min or a single episode of apnea that requires bag and mask ventilation)
- Hypoxemia (FiO2 >0.5 to maintain SpO2 90% to 94%)
- Severe respiratory distress characterised by retractions, moaning sounds or nasal flaring (defined as Silverman score >6) ***(Silverman and Anderson,1956).***
- Pulmonary haemorrhage and Cardiopulmonary arrest needing chest compressions ***(Shi and De Luca, 2019).***

13. Laboratory investigations

- Complete blood picture (CBC),C- reactive protein (CRP) and Venous blood gases, using a POC Siemens RAPID Point 500 blood gas system,Radiometer Medical ApS,Denmark ***(Allardet et al., 2017)***.

14. Radiological investigation

A. Chest X-ray with radiological assessment of grades of RDS.

B. Echocardiography : Two dimensional Echocardiography will be done using Vivid 9,GE Ultrasonography machine (Norway) with 6 MHz transducer frequency.To assess any structural cardiac anomalies, the patency of ductus arteriosus, right ventricular output (RVO), left ventricular output (LVO), and superior vena cava (SVC) flow.

C. Transcranial ultrasonography by; Samsong Medison Co ,Korea. Doppler applied to the major cerebral arteries to provide an estimate of cerebral blood flow .

D. Assessment of pre-prandial superior mesenteric artery (SMA) velocity and volume of blood flow with Doppler sonography by; Samsong Medison Co ,Korea.

15. Statistical Analysis: Numerical data will be summarized using mean and standard deviations or medians and inter quartile ranges. Qualitative data will be presented as count and percentage, p-value <0.05 will be considered significant.

16. Statistical Package: Statistical analysis will be performed with statistical package for social science (SPSS)

17. Ethical Considerations: A written informed consent will be taken from the parents or legal guardians before enrolment, after fully explaining to them the nature of the study. The approval of the Research Ethics Committee at Ain Shams University will also be obtained.

4. REFERENCES

1. **Abdel-Hady H, Matter M, Hammad A, El-Refaay A, Aly H (2008):** Hemodynamic Changes During Weaning From Nasal Continuous Positive Airway Pressure. Pediatrics ;122(5): 1086–1090.
2. **Allardet-Servent J, Lebsir M, Dubroca C, Fabrigoule M, Jordana S, Signouret T, Castanier M, Thomas G, Soundaravelou R, Lepidi A, Delapierre L, Penaranda G, Halfon P, Seghboyan JM (2017):** Point-of-Care Versus Central Laboratory Measurements of Hemoglobin, Hematocrit, Glucose, Bicarbonate and Electrolytes: A Prospective Observational Study in Critically Ill Patients. PLoS One. Jan 10;12(1):0169593.
3. **Ballard J, Khoury J, Wedig K, Wang L, Eilers-Walsman B, Lipp R (1991):** New Ballard Score, expanded to include extremely premature infants. J Pediatr; 119(3):417-423.
4. **Beker F, Rogerson SR, Hooper SB, Wong C, Davis PG (2014):** The effects of nasal continuous positive airway pressure on cardiac function in premature infants with minimal lung disease: a crossover randomized trial. J Pediatr; 164:726-9.
5. **De Luca D and Dell'Orto V (2016):** Non-invasive high-frequency oscillatory ventilation in neonates: review of physiology, biology and clinical data. Archives of Disease in Childhood - Fetal and Neonatal Edition;101(6): 565–570.
6. **Hermansen CL and Mahajan A (2015):** Newborn Respiratory Distress. Am Fam Physician;92(11):994-1002.
7. **Jobe A and Bancalari E (2001):** Bronchopulmonary dysplasia. Am J Respir Crit Care Med; 163:1723-1729.
8. **Khan J, Sundaram V, Murki S (2017):** Nasal injury and comfort with jet versus bubble continuous positive airway pressure delivery systems in preterm infants with respiratory distress. Eur J Pediatr ;176: 1629–1635.
9. **Mahmoud RA, Roehr CC, Schmalisch G (2011):** Current methods of non-invasive ventilatory support for neonates;12(3):196–205.
10. **Mukerji A and Dunn M (2016):** High-Frequency Ventilation as a Mode of Noninvasive Respiratory Support. Clinics in Perinatology; 43(4): 725-740.
11. **Muniraman HK, Song AY, Ramanathan R, Fletcher KL, Kibe R, Ding L, Lakshmanan A, Biniwale M(2019):** Evaluation of Oxygen Saturation Index Compared With Oxygenation Index in Neonates With Hypoxemic Respiratory Failure. JAMA Netw Open ;2(3): 191179.
12. **Permall DL, Pasha AB, Chen Xq (2019):** Current insights in non-invasive ventilation for the treatment of neonatal respiratory disease. *Ital J Pediatr;* 45: 105.
13. **Price AM, Plowright C, Makowski A, Misztal B(2008):** Using a high-flow respiratory system (Vapotherm) within a high dependency setting. Nurs Crit Care Nov-Dec;13(6):298-304.
14. **Shi Y and De Luca D (2019):** Continuous positive airway pressure (CPAP) vs noninvasive positive pressure ventilation (NIPPV) vs noninvasive high frequency oscillation ventilation (NHFOV) as post-extubation support in preterm neonates: protocol for an assessor-blinded, multicenter, randomized controlled trial. BMC Pediatrics; 19(1):256-270.
15. **Silverman W and Anderson D (1956):** A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. Pediatrics;17:1-10.
16. **Yoder BA, Manley B, Collins C, Ives K, Kugelman A, Lavizzari A, McQueen M (2017):** Consensus approach to nasal high-flow therapy in neonates. Journal of Perinatology; 37(7): 809–813.
17. **Zhu XW, Shi Y, Shi LP, Liu L, Xue J, Ramanathan R, NHFOV Study Group (2018):** Non-invasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: Study protocol for a multi-center prospective randomized controlled trial. Trials; 19(1): 319