STUDY DETAILS

Comparison of X-Breathe HFNC NeoTM high-flow nasal cannula versus standard continuous positive airway pressure in late preterm neonates with respiratory distress

Intervention

Brief Name

The interventions in this study include the XBreathe Neo™ High-Flow Nasal Cannula (HFNC) and the standard Continuous Positive Airway Pressure (CPAP) device routinely used at Bandung Kiwari General Hospital (the trademark of the CPAP device is not disclosed due to confidentiality reasons).

Why

Non-invasive respiratory support plays a critical role in managing neonatal respiratory insufficiency, helping to reduce the need for invasive mechanical ventilation and its associated complications. Among the commonly used non-invasive modalities, High-Flow Nasal Cannula (HFNC) and Continuous Positive Airway Pressure (CPAP) are widely utilized for neonatal respiratory support.

The main goal of current clinical trial is to test the efficacy and safety of a new product produced in Indonesia, namely XBreathe Neo^{TM} HFNC. As a comparison, CPAP was applied in control arm. The rationale of utilizing CPAP in the control arm is due to major neonatal guidelines, including those from the American Academy of Pediatrics (AAP) and European Consensus Guidelines on the Management of RDS (2022), recommend CPAP as the initial non-

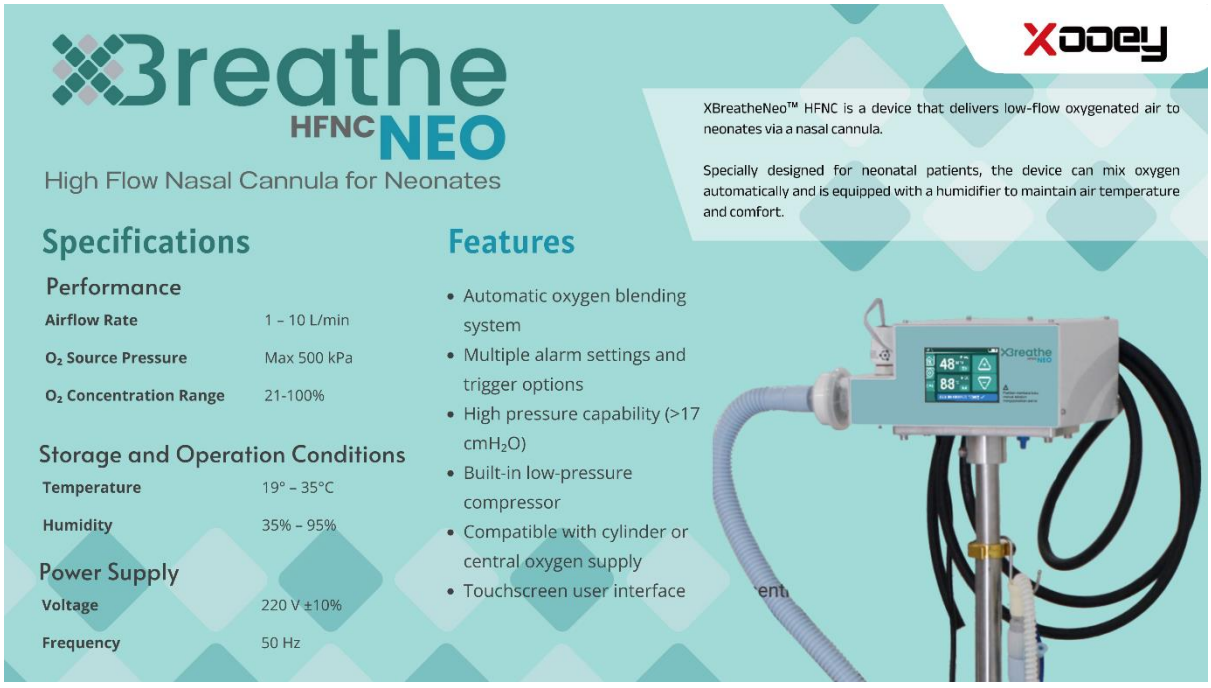
invasive modality for preterm infants with respiratory distress. HFNC is generally reserved as an alternative when CPAP is not tolerated or during weaning [Sweet et al., Neonatology, 2022]. CPAP has also been routinely used to as first line non-invasive respiratory support treatment in Bandung Kiwari Hospital.

Reference:

Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2022 Update. Neonatology. 2023;120(2):183-204. doi:10.1159/000528423

What

The brochure of the device used in the study can be seen below.



Study Protocol

RECRUITMENT

Neonates admitted to Neonates Intensive Care Unit (NICU) of Bandung Kiwari General Hospital from October to December 2022 with following criteria: 1) gestational age ≥ 28 weeks, 2) birth weight exceeding 1500 grams, 3) diagnosed with respiratory distress syndrome.

Patients were excluded if: 1) had experienced severe respiratory distress, 2) were likely to develop respiratory failure requiring invasive ventilation, 3) declined to participate in the study.

Informed consents were obtained from patients' parents or legal representatives before the study commenced.

SAMPLE SIZE AND RANDOMIZATION

Patients were recruited through consecutive sampling. The number of patients to be recruited was calculated using following formula

$$n = \frac{Z\alpha/_2{}^2 \times p \times (1-p)}{d^2}$$

Where:

n : minimum required sample size

Zα : Z-score for the confidence level (1.96 for 95% confidence)

p : expected proportion (prevalence or incidence rate)

d : margin of error (acceptable difference from the true proportion)

The value of *p* was calculated based on the prevalence of treatment failure following HFNC or CPAP oxygenation in neonates. A study by Manley et al. (2019) reported that the rate of treatment failure within 72 hours after HFNC and CPAP in term infants (gestational age >31 weeks) was 14.5% and 8.0%, respectively [5].

The precision estimate was derived from the confidence interval for treatment failure reported in a meta-analysis by Dopper et al. (2023), which ranged from 8.1% to 35.1% [2]. Accordingly, the estimated precision was calculated by dividing the confidence interval range by 2, resulting in 13.5%.

Applying the lowest expected proportion of treatment failure (8.0%) and a precision of 13.5%, the minimum required number of patients is:

$$n = \frac{Z_{\alpha/2}{}^2 \times p \times (1-p)}{d^2}$$

$$n = \frac{1.96 \times 0.08 \times 0.92}{0.135^2}$$

$$n = 7{,}915 \approx 8 \text{ patients} \approx 10 \text{ patients}$$

The minimum required sample size was 8 patients, which was rounded up to 10 patients. Considering a 10% drop-out rate, the final number of patients to be recruited was 11.

Patients were randomized to receive HFNC or CPAP using simple computer-generated randomization based on their identification numbers.

PROCEDURE

A. High-Flow Nasal Cannula (HFNC)

The initial HFNC setting consisted of an airflow rate of 5 liters per minute (LPM). The fraction of inspired oxygen (FiO_2) was adjusted to maintain peripheral oxygen saturation (SpO_2) between 91% and 95%.

Airflow was increased by 1 LPM, up to a maximum of 7 LPM, if any of the following criteria were met:

1. An increase in FiO_2 by 10% above the initial FiO_2.

2. An increase in the Downe Score by 1 point from baseline.

Airflow was reduced by 0.5 to 1.0 LPM once all of the following conditions were met:

1. $FiO_2 < 30\%$
2. Stable SpO_2 between 91% and 95%
3. Absence of respiratory distress (Downe Score < 4)

Once these parameters remained stable, neonates were gradually weaned from HFNC.

B. Continuous Positive Airway Pressure (CPAP)

The initial Positive End-Expiratory Pressure (PEEP) was set to 7 cmH_2O. PEEP was reduced stepwise by 1 cmH_2O when all of the following conditions were met:

1. Downe Score < 4
2. SpO_2 maintained between 91% and 95% with $FiO_2 < 30\%$
3. Respiratory rate within the normal range for neonatal age
4. Minimal or no episodes of apnea, bradycardia, or desaturation

Who: All procedures were delivered by neonatologist and intensivist.

OUTCOME MEASURE

The assessed outcomes included peripheral capillary oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), respiratory rate (RR), heart rate (HR), and the Downe Score. These parameters were recorded every 15 minutes during the first 3 hours, and subsequently every 2 hours for a total observation period of 48 hours. SpO_2, RR, and HR were measured using the sensors integrated into the multiparameter patient monitors available in the NICU. FiO_2 levels were recorded directly from the CPAP or HFNC devices.

Dawne Score was measured based on clinical findings. It is a 5 items score, scored from 0 to 2. The criteria are as follow:

Parameter	Score 0	Score 1	Score 2
Respiratory rate	< 60 breaths / min	60 – 80 breaths/min	>80 breaths/min or irregular
Cyanosis	None	With oxygen	Despite oxygen
Air entry	Normal	Decreased	Barely audible
Grunting	None	Audible with stethoscope	Audible without stethoscope
Chest retraction	None	Mild to moderate	Severe

Interpretation:

Score	Severity	Clinical Significance
0 – 3	Mild	May need observation or minimal support
4 – 6	Moderate	Requires intervention
7 – 10	Severe	Requires intensive support or ventilation

Adverse events were observed during the duration of the study for 48 hours.

Statistical Analysis

Independent T-test or Mann-Whitney U test was used to assess significant differences between groups for continuous outcomes, depending on the normality of the data. One-sample T-test or Wilcoxon signed-rank test was used to compare the sample values against the target values, depending on the data distribution. Dichotomous outcomes were analysed using the Chi-square test. Shapiro-Wilk test was performed to evaluate the normality of the data distribution. Statistical analyses were conducted using GraphPad Prism 10.0.0 for Windows (GraphPad Software, Boston, Massachusetts, USA; www.graphpad.com).

Who: Statistical analysis were conducted by a medical statistician.