

Protocol title: *Heated, Humidified High-Flow Nasal Cannula vs Nasal CPAP for Respiratory Distress Syndrome of Prematurity.*

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Rationale and Objective:

Heated, Humidified High Flow Nasal Cannula (HHHFNC) gained increasing popularity as respiratory support for newborn infants thanks to ease of use and improved patients' comfort.

However, its role as primary therapy for respiratory distress syndrome (RDS) of prematurity needs to be further elucidated by large, randomized clinical trials.

Being nCPAP currently considered the golden standard for early respiratory management and considering the benefits associated with HHHFNC compared to nCPAP the objective the current study is to evaluate whether HHHFNC provides respiratory support noninferior to nCPAP when applied exclusively as primary approach to mild to moderate RDS in preterm infants > 28 weeks of GA.

Study Design: A prospective, monocentric, unblinded, randomized, noninferiority trial; a noninferiority margin (NIM) 10%.

Patients

Inclusion criteria:

1. GA $\geq 29^{+0}$ and $< 37^{+0}$ weeks;
2. mild to moderate RDS requiring non-invasive respiratory support, characterized by Silverman score ≥ 5 or fraction of inspired oxygen ($F_{I}O_2$) > 0.3 for target saturation of peripheral oxygen (SpO_2) 88-93%;
3. parental consent obtained.

Exclusion criteria:

1. severe RDS requiring early intubation according to the AAP guidelines for neonatal resuscitation;
2. major congenital anomalies that might affect respiratory outcomes;
3. severe intraventricular haemorrhage (IVH).

Methodology

Randomization:

A block-randomization will be applied, with a block size of 4. Infants were stratified according to GA: from 29^{+0} to 32^{+6} weeks, from 33^{+0} to 34^{+6} weeks and from 35^{+0} to 36^{+6} weeks. Infants born from multiple gestations will be assigned by individual randomization. A sequentially numbered, sealed, opaque envelope of the appropriate GA stratum will be opened by clinicians if all the criteria for enrollment are matched.

Study intervention: infants will be randomized to receive either HHHFNC at 4-6 lpm or nCPAP at 4-6 cmH₂O.

All the infants enrolled will have a chest radiograph before starting the respiratory support. The infants assigned to HHHFNC will be supported by Vapotherm (Stevensville, MD). Nasal cannula size will be chosen, according to manufacturer suggestions (occupying approximately 50% of the nares). HHHFNC will be started at a flow of 4-6 lpm and increased to a maximum of 6 lpm if $F_{I}O_2$ increases >0.1 of the starting value or for intensification of respiratory distress assessed by Silverman score.

NCPAP will be provided by SiPAP (Viasys Healthcare, Palm Springs, CA). The starting pressure will be set at 4-6 cmH_2O and increased up to 6 cmH_2O according to the same criteria for altering HHHFNC flow. Infants can be shifted to biphasic CPAP mode in case of >4 episodes of apnea per hour or >2 episodes per hour requiring positive pressure ventilation (PPV) or if deemed by clinicians because of increased work of breathing. Biphasic CPAP will be set with a starting rate of 30/min, inspiratory time of 0.7-1 sec and a mean airway pressure 6-8 cmH_2O .

Criteria for administering Surfactant : in case of increased $F_{I}O_2 >0.35$ to target SpO_2 86-93%; Curosurf-Chiesi Farmaceutici, Parma, Italy; 200 mg/kg given by INSURE technique.

Criteria for intubation and mechanical ventilation:

- Persistent $F_{I}O_2 >0.40$ to target SpO_2 86-93% after surfactant administration;
- Severe apnea (apnea episodes >4 per hour or >2 per hour requiring PPV);
- Persistent $PaCO_2 >70$ mmHg and $pH <7.20$ despite application of non-invasive respiratory support.

Extubation criteria:

- $F_{I}O_2 <0.30$ to target SpO_2 ;
- $PaCO_2 <65$ mmHg and $pH >7.25$;
- Adequate spontaneous breathing drive.

Weaning from non-invasive respiratory support: HHHFN flow will be decreased by 1 lpm or nCPAP pressure by 1 cmH₂O if F₁O₂ <0.30 to target SpO₂ and minimal or no signs of respiratory effort. The respiratory support will be discontinued for flow ≤ 2 lpm or pressure ≤ 2 cmH₂O.

Primary outcome: respiratory support failure determined by the need of intubation and mechanical ventilation within 72 hours from the beginning of the study mode.

Secondary Outcomes:

Respiratory outcomes: days on respiratory support, days on non-invasive respiratory support and days on supplemental oxygen; days of caffeine treatment; need of surfactant; rate of air-leaks and bronchopulmonary dysplasia (BPD).

Other secondary outcomes: rate of sepsis (confirmed by positive blood culture), necrotizing enterocolitis, patent ductus arteriosus, IVH, retinopathy of prematurity, death and the combined outcome including all the previous, air-leaks and BPD. Secondary outcomes also included: days for full-enteral feeding (≥ 120 ml/kg/day), body weight at discharge, exclusive breast feeding at discharge and length of hospitalization.

Follow-up: data will be collected until discharge home.

Statistical Analysis:

According to a retrospective analysis for the 2-year period 2009-2010, the risk of failure on nCPAP in our centre for infants > 28 weeks of GA was 15%. The sample size was computed considering a noninferiority margin (NIM) for HHHFNC of 10% points above the failure rate of nCPAP, $p= 0.05$ and a power of 80%. We determined that 316 patients were required to assess noninferiority for HHHFNC with a 1-tailed 95% confidence interval (equivalent to a 2-tailed 90%CI).

The 95%CI of the risk difference or difference in medians (Hodges-Lehmann) will be calculated for all the outcomes (SAS Institute, Inc. 2008. SAS/STATVR 9.2). Dichotomous outcomes will be compared by χ^2 tests. Continuous outcomes will be compared by using the appropriate parametric (Student's t-test) or not parametric (Mann-Whitney Rank-sum test) test.

A posteriori, a logistic model will be applied to detect factors possibly affecting the probability of failure. The covariates included into the logistic model will be : respiratory support modes, gestational age strata, sex, birth weight <1500g, high risk pregnancy (including chorioamnionites, prolonged premature rupture of membranes, gestosis, and placental abruption), antenatal steroids and multiple gestations.

Duration of the Project: from January 2012; expected duration about 2,5 years

Ethics: The ethical committee approval of Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy was obtained prior to the study.

Informed Consent Forms: Parental consent was obtained before patients' enrolment.