Short term effects of synchronized vs. non-synchronized NIPPV in preterm infants. A randomized crossover study.

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Respiratory problems are one of the major issues to deal with in preterm newborns. Because of the immaturity of respiratory mechanisms and structures the use of supporting devices is often necessary. These include both conventional mechanical ventilation (MV) techniques, which require the use of an endotracheal tube, as well as non-invasive ventilation (NIV) techniques that use softer ventilator-patient interfaces. Increasing attention is paid to the latter ones as less aggressive and associated with better outcomes both in terms of mortality and short and long-term complications, such as bronchopulmonary dysplasia (BPD).

Nasal intermittent positive pressure ventilation (NIPPV) is a NIV technique in which newborn airways are kept open between two pressure levels: peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP). The frequency and duration of each phase are defined by setting the inspiratory and expiratory times or the ventilation rate. This technique has already shown its superiority in terms of reduced duration of MV, reduced necessity of intubation, decreased failure of extubating and reduced prevalence of BPD if compared with non-invasive techniques based on continuous pressure support, such as CPAP. It should be specified that the ventilation rate on NIPPV does not reflect the real respiratory rate of the newborn, as the ventilator supplies the PIP regardless of newborn respiratory efforts. To reproduce a more physiological and gentle ventilation new devices able to detect newborn respiratory efforts and consequently supply a PIP have been developed so as to synchronize the ventilation rate with the respiratory rate of the newborn. Some authors have already demonstrated the benefits of using a synchronized NIV technique in terms of extubating success rate, BPD prevalence and mortality and neurocognitive development. The devices used for synchronization can identify newborn respiratory effort by detecting variation in flow or pressure.

While in MV the exact beginning of inspiration can be detect through a continuous monitoring of pressure or through the precise interception of inspiratory and expiratory flow some difficulties occur in NIV where, as a consequence of the impossibility to detect expiratory flow, the moment of the exact beginning of spontaneous inspiration is hard to identify. Various techniques have been elaborated to overcome this problem such as diaphragmatic contraction sensor (considered to be poorly precise and too invasive) and inspiratory flow sensor able to achieve good synchronization with newborn respiratory efforts despite the high intrinsic losses of the NIV circuit.

The use of a synchronized NIV technique would allow a more physiological respiratory support, reducing respiratory fatigue and improving newborn compliance. Despite these premise, the diffusion of synchronized NIPPV in neonatal intensive care units and works on its efficacy are too limited. Our study aims to evaluate the short-term effects of synchronized NIPPV (sNIPPV) vs non-synchronized NIPPV on the major cardio-respiratory variables.
STUDY DESIGN
randomized cross-over study (figure 1)

OUTCOMES
Primary outcome: frequency of cardio-respiratory events during sNIPPV vs NIPPV.
Secondary outcome includes:
- frequency of NIV failure (necessity of endotracheal intubation)
- $\text{O}_2$, PEEP, PIP needing to maintain in a transcutaneous oxygen saturation between 90 and 95%
- cardiorespiratory parameters
- intestinal and cerebral regional oximetry measured via NIRS
- newborn pain score evaluation
- newborn non-invasive compliance

POPULATION UNDER STUDY
All newborns needing NIV ventilation support and with all following characteristics:
- gestational age at birth < 32 weeks
- first approach to NIV ventilation (primary or after-extubating)
- parent's informed consent

EXCLUSION CRITERIA
- presence of sepsis (clinical or laboratory confirmed)
- neurological problems (including IVH > 2° grade)
- cardiac problems (including PDA hemodynamically significance)
- genetic abnormalities
- congenital anomalies

NUMBER OF PATIENTS
The number of patients to be enrolled is calculated based on a predicted difference of 30% in cardio-respiratory events between the two ventilation modalities. Assuming a mean of 5 and a SD of 1.5 events/hour (based on available literature data), the number of patients to be enrolled is 30, to obtain an 80% power and a significance threshold of 0.05.

STUDY DESIGN
The decision to use a NIV support is based on clinical evaluation. Enrolled newborns will be maintained in NIPPV for 2 hours (adaptation phase). Then, according to a block randomization list previously elaborated, they are alternatively assigned to the NIPPV or sNIPPV arm for a time of 4 hours each. During the whole study duration (including adaptation phase) all patients will be continuously monitored with a cardiorespiratory monitor. The instrument records thoracic impedance (through which respiratory frequency is calculated), ECG (to calculate heart rate) and pulse-oximetry (to obtain heart rate and blood oxygen saturation). The first hour of each NIPPV/sNIPPV phase will be considered “adaptation phase” and will be excluded from the analysis. Pain and compliance scales will be filled in every 60 minutes. In case of endotracheal intubation due to NIV failure ($\text{FiO}_2 > 40\%$ and/or apnea episodes and/or increasing $\text{pCO}_2$) the study will be interrupted.

MONITORING
Nurse staff will continuously monitor patients to avoid biases due to device wrong positioning
DATA
For each patient enrolled the following variables will be collected:
- gestational age at birth
- birth weight
- delivery type
- APGAR at 1/5 minutes (and 10 minutes if available)
- steroid prenatal prophylaxis
- surfactant administration
- type and duration of MV previously administered (if any)
- type and duration of NIV previously administered (if any)
- corrected gestational age at enrolling
- caffeine doses administered (if any)
- $\text{FiO}_2$ maintained during monitoring
- EGA values at start and end of monitoring
- Neonatal Pain Scale score

CARDIO-RESPIRATORY VARIABLES
The modality of ventilator support will be evaluated according to the following variables:
- $\text{FiO}_2$ to maintain $\text{SatO}_2$ 90-95% (as weighted mean)
- NIV failure and endotracheal intubation
- Need to change NIV modality <3 hours
- Number of blood oxygen desaturation ($\text{SatO}_2 < 80\%$ for at least 4 seconds)
- Number of apneas (as absence of thoracic movements for at least 20 seconds or at least 5 seconds if associated to desaturation or bradycardia)
- Number of episodes of bradycardia (as heart rate <80 bpm)

RESULTS INTERPRETATION
The main result will be the difference in cardio-respiratory events during sNIPPV versus NIPPV. Tolerance to each of the two NIV modalities will be evaluated by evaluating the number of failure episodes and of cardio-respiratory events and analysing the scores for individual compliance and pain. The individual need for oxygen under the two modalities of NIV will be evaluated as a known risk factor for premature retinopathy and various other complications.

STATISTICAL ANALYSES
Descriptive variables will be analyzed in function of their distribution. T student test or Mann Whitney U test in case of continuous variables (if normally or not normally distributed respectively) and chi-squared or fisher test for qualitative ones. All test will be two-sided with a significance threshold of 0.05.

EXPECTED RESULTS
Identifying the best NIV modality for preterm newborns at their first approach to NIV ventilation support, on the bases of cardio-respiratory events reduction and $\text{FiO}_2$ request.