Short term effects of synchronized vs. non-synchronized NIPPV in preterm infants: study protocol for an unmasked randomized crossover trial.

Francesco Cresi
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Federica Chiale (federica.chiale@gmail.com)
Universita degli Studi di Torino https://orcid.org/0000-0003-2857-7453
Elena Maggiora
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Silvia Maria Borgione
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Mattia Ferroglio
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Federica Runfola
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Giulia Maiocco
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Chiara Peila
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Enrico Bertino
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
Alessandra Coscia
Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino

Study protocol

Keywords: Non-invasive ventilation, NIPPV, SNIPPV, Synchronization, Cardiorespiratory events, Preterm infants, RDS

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Short term effects of synchronized vs. non-synchronized NIPPV in preterm infants: study protocol for an unmasked randomized crossover trial.

Francesco Cresi[1], Federica Chiale[1,2], Elena Maggiora[1], Silvia Maria Borgione[1], Mattia Ferroglio[1], Federica Runfola[1,2], Giulia Maiocco[1], Chiara Peila[1], Enrico Bertino[1], Alessandra Coscia[1]

francesco.cresi@unito.it; federica.chiale@gmail.com; elena.maggiora@gmail.com; silvia.borgione@unito.it; ferroglio.mattia@gmail.com; federica.runfola@yahoo.it; giulia.maiocco@edu.unito.it; peila.chiara@gmail.com; enrico.bertino@unito.it; alessandra.coscia@unito.it.

Correspondence:

Corresponding Author:

Federica Chiale

Neonatology and Neonatal Intensive Care Unit, University of Turin, Turin, Italy

Via Ventimiglia, 3 - 10126, Turin, Italy,

Tel. +390113134437

federica.chiale@gmail.com

Abstract

Background:

Non-invasive ventilation (NIV) has been recommended as the best respiratory support for preterm infants with respiratory distress syndrome (RDS). However, the best NIV technique to be used as first intention in RDS management is not yet established.

Nasal intermittent positive pressure ventilation (NIPPV) may be synchronized (SNIPPV) or non-synchronized to the infant's breathing efforts.

The aim of the study is to evaluate short-term effects of SNIPPV vs NIPPV on cardiorespiratory events, trying to identify the best ventilation modality for preterm infants at their first approach to NIV ventilation support.

Methods:

An unmasked randomized crossover study with two treatment phases was designed. All newborn infants < 32 weeks of gestational age with RDS needing NIV ventilation as first intention or after extubation will be consecutively enrolled in the study and randomized to the NIPPV or SNIPPV arm. After stabilization, enrolled patients will be alternatively ventilated with two different techniques for two time frame of 4 hours each. NIPPV and SNIPPV will be administered with the same ventilator and the same interface, maintaining a continuous assisted ventilation without patient's discomfort.

During the whole study duration, patient cardiorespiratory data and data from the ventilator will be simultaneously recorded using a polygraph connected to a computer.

The primary outcome is the frequency of episodes of oxygen desaturation. Secondary outcomes are number of cardiorespiratory events, FiO2 necessity, newborn pain score evaluation, synchronization index and thoracoabdominal asynchrony. The sample size was calculated at 30 patients.

Discussion:

It is known that NIPPV produces a percentage of ineffective acts due to asynchronies between ventilator and infant's breaths. On the other hand, an ineffective synchronization could increase work of breathing. Our hypothesis is that an efficient synchronization could reduce the respiratory work and increase the volume per minute exchanged without interfering with the natural respiratory rhythm of the patient with RDS. The results of this study will allow us to evaluate the effectiveness of the synchronization, demonstrating whether SNIPPV is the most effective non-invasive ventilation mode in preterm infants with RDS at their first approach to NIV ventilation.

Trial registration: ClinicalTrials.gov, NCT03289936. Registered on 09/21/2017.

Keywords: Non-invasive ventilation, NIPPV, SNIPPV, Synchronization, Cardiorespiratory events, Preterm infants, RDS

Background

Respiratory problems are one of the major issues to deal with in preterm infants (1). 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) (2,3).

Nasal intermittent positive pressure ventilation (NIPPV) is a NIV technique in which infant airways are kept open between two pressure levels: peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP) (4,5). 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 extubation failure and reduced prevalence of BPD if compared with non-invasive techniques based on continuous pressure support, such as continuous positive airway pressure (CPAP) (6). Recent meta-analyses of studies where NIPPV has been used as an alternative to CPAP following extubation show that it reduces need for re-ventilation and air leaks but without any reduction in BPD (7): there is insufficient evidence to recommend NIPPV as primary mode of respiratory support in the delivery room (1).

It should be specified that the ventilation rate on NIPPV does not reflect the real infant's spontaneous respiratory rate (RR), as the ventilator supplies the PIP regardless of respiratory efforts. In order to reproduce a more physiological and gentle ventilation, new devices able to detect infant's respiratory effort and consequently supply a PIP have been developed, synchronizing the ventilation rate with infant's RR.

The devices used for synchronization can identify infant's respiratory effort by detecting variation in flow or pressure. While in MV the exact beginning of inspiration can be detected 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.

Recently, a new type of NIV ventilator equipped with a pressure sensor has been put on the market. The software of this ventilator is able to calculate the flow according to the pressure variations of the circuit and to capture the flow variations induced by spontaneous breathing allowing a synchronization of the flow with the patient's respiratory acts (8).

The use of a synchronized NIV technique would allow a more physiological respiratory support, reducing respiratory fatigue and improving infant’s compliance. Despite these premises, the diffusion of synchronized NIPPV in neonatal intensive care units (NICUs) and works on its efficacy are limited (9).

Some authors have already demonstrated the benefits of using a synchronized NIV technique in terms of extubating success rate, BPD prevalence, mortality and neurocognitive development (2,8). Synchronized NIPPV (SNIPPV) seems more effective than NIPPV and NCPAP in reducing need for intubation in respiratory distress syndrome (RDS), in improving the success of extubation and in treating apnea of prematurity, with a reassuring absence of relevant side effects (7,8,10). Synchronised NIPPV delivered through a ventilator can reduce extubation failure but may not confer long-term advantages such as reduction in BPD (1). Other reported advantageous aspects of SNIPPV include improved thoracoabdominal synchrony, reduced work of breathing (WOB) and reduced need of intubation (5,7,11).

It has already been shown that SNIPPV is more effective than NIPPV and CPAP in reducing the number of desaturations and apnoea in preterm infants undergoing CPAP treatment for prematurity apnoea (12). However, the effectiveness of SNIPPV compared to NIPPV in preterm infants with RDS is still not completely clear.

Our study protocol was designed to evaluate the short-term effects of SNIPPV vs NIPPV on the major cardio-respiratory variables, trying to identify the best ventilation modality for preterm infants at their first approach to NIV ventilation support, on the bases of cardio-respiratory events reduction and fraction of inspired oxygen (FiO2) request.

Methods

Aims

Evaluate short-term effects of SNIPPV vs NIPPV in a group of preterm infants on cardiorespiratory events at their first approach to NIV ventilation as first intention (soon after birth) or after extubation.

Study design and setting

The study has been designed as an unmasked randomized crossover study. It will involve the neonatal intensive care unit (NICU) of the University of Turin.

Inclusion criteria

All newborn infants with RDS needing NIV ventilation (NIPPV or SNIPPV) as first intention or after extubation and with all following characteristics will be consecutively enrolled in the study:

- gestational age (GA) at birth <32 weeks
- first approach to NIV ventilation (primary or after extubation)
- parental written consent

Exclusion criteria

The following are the study exclusion criteria:

1. Neurological (including IVH > 2° grade) or surgical diseases

2. Sepsis (clinical or laboratory confirmed)

3. Chromosomal or genetic abnormalities

4. Major malformations and congenital anomalies

5. Cardiac problems (including hemodynamically significant PDA)

6. Contraindication to NIV (i.e. nasal trauma and gastrointestinal surgery within the previous 7 days).

Recruitment and randomization

Informed written consent will be signed by both parents, and sufficient time will be allowed for consent. Non-Italian-speaking parents will only be asked for their consent if an adult interpreter is available. Trust interpreter and link worker services will be used to support involvement of participants whose first language is not Italian.

The decision to use a NIV support will be based on clinical evaluation. At starting of NIV, eligible patients will be allocated to one of the two arms (NIPPV or SNIPPV) by block randomization. A custom software will be used to obtain a casual sequence to randomize patients in both arms, creating a balance between patients needing NIV as first intention or after extubating.

After 2 hours of stabilization (stabilization phase) in NIV mode assigned by randomization, enrolled patients will be alternatively ventilated with two different techniques for two time frame of 4 hours each. In case of needing surfactant, the stabilization phase will be 4 hours after administration.

Infants will be kept supine throughout the study. During the whole study duration (including stabilization phase), all patients will be continuously monitored with a multiparametric monitor, recording also data from the ventilator. The first hour of each NIPPV/SNIPPV time frame will be

considered as wash-out phase and named “adaptation phase”: data recorded during this phase will be excluded from the analysis. Milk meals will be administered during the adaptation phase.

Pain and compliance scales will be filled in by nurses every 60 minutes. EGA values will be recorded at the end of the stabilization phase, at the end of Phase A (first NIV modality) and Phase B (second NIV modality).

Patients will drop out of the study in case of:

1. NIV failure criteria: $FiO_2 > 40\%$, $pH < 7.2$, $pCO_2 > 65mmHg$, ≥ 3 episodes of desaturations (transcutaneous O_2 saturation ($SatO_2$ TC) < 80%) per hour, ≥ 3 episodes of apnea (> 20 seconds) and/or bradycardia (heart rate (HR) < 80 beats per minute (bpm)) per hour, Silverman score > 6. Necrotizing enterocolitis, bowel perforation, and hemodynamic instability are indications of NIV failure (13)
2. Air leak syndrome (i.e. pneumothorax)
3. Needing of invasive procedures during the study
4. Needing of surfactant during the study
5. Development of hemodynamic instability or surgical problems during the study
6. Death

Data obtained from dropouts (patients who drop out of the study) will be analysed separately.

After 8 hours of study, each patient will be ventilated with the best NIV modality according to clinical data and cardio-respiratory parameters observed during the study.

The design of the study is outlined in Figure 1.

<u>Techniques</u>

NIV ventilator

NIPPV is a non-invasive ventilation technique in which PIP administration is not synchronized with infant's respiratory efforts. SNIPPV is a non-invasive ventilation technique in which PIP administration is synchronized with infant's respiratory efforts.

NIPPV and SNIPPV will be delivered using a Giulia® neonatal ventilator via nasal prongs (Ginevri Medical Technologies, Rome, Italy). With this device, clinicians can switch from NIPPV to SNIPPV mode and vice versa without changing the circuit and the ventilation interface avoiding discomfort for the patient. The size of the nasal prongs will be determined by the infant's weight and characteristics to minimize nasal leak as per the manufacturer's recommendation.

In SNIPPV mode, the synchronization will be achieved through an algorithm based on flow detection throw a fixed orifice pneumotachograph (2.5 mm inner diameter—dead space 1 mL) interposed between the prongs and the Y piece (flow-SNIPPV).

The optimal NIV setup will be decided by the clinicians and individualized for each patient during the stabilization phase in order to obtain the lowest FiO2 levels necessary to reach SatO2 TC of 90-94%, then the values of PEEP, PIP, backup RR, flow and inspiratory time will be kept constant during phases A and B.

Polygraphy

The Embletta® MPR PG (PG (Multi Parameter Recorder - Polygraphy) - XS is a multiparametric polygraph to record patient's CG trace (to calculate HR), FiO2, pulse-oximeter (to obtain HR and SatO2 TC), respiratory curve (thoracic impedance, through which RR is calculated). The Embletta will be also interfaced with Giulia® ventilator by using a custom interface (Ginevri Medical

Technologies, Rome, Italy) to obtain from Giulia® ventilator three analogue outputs channels (trigger, pressure, flow).

Data from Embletta will be analysed by a designed software provided by the manufacturer.

Monitoring and data collection

Data on respiratory support and overall clinical status will be collected from enrolment to discharge.

Data will be recorded consecutively by polygraph from enrolment to the end of study.

All data to be collected will be obtained from the clinical records and from the Embletta® MPR PG-XS. Data will be recorded on a database specifically designed for this study. Access to the database will be password protected. Participants will be identified by trial number only. All data recorded throughout the study period are listed in Table 1.

A statistical investigator without clinical role will be identified to monitor and oversee the trial.

Cardiorespiratory events

Cardiorespiratory events are defined as episodes of apnea lasting more than 20 seconds or over 5 seconds if followed by desaturation or bradycardia and/or episodes of desaturation with blood oxygen saturation below 80% for 4 seconds or more and/or episodes of bradycardia with HR below 80 bpm.

Outcomes

The primary outcome of the study is the frequency of episodes of desaturation.

Secondary outcomes are listed below:

1. Number of cardiorespiratory events (apnea, bradycardia, oxygen desaturation)

2. FiO2 needing during SNIPPV vs NIPPV monitoring to maintain SatO2 TC between 90 and 94%, defined as mean fraction of inspired oxygen, expressed in percentage.
3. Newborn pain score evaluation during SNIPPV vs NIPPV monitoring, using Neonatal Pain Scale Score.
4. Synchronization index, defined as the percentage of spontaneous breaths supported by ventilator.
5. Patient-ventilator concordance, defined as the time between the onset of the patient's inspiratory effort and mechanical inflation in synchronized ventilation.
6. Thoracoabdominal asynchrony, defined as the phase difference between thoracic and abdominal impedance.

Dropout patients will be considered to establish frequency of NIV failure, NIV weaning and need of surfactant during each phase of the study.

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.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of enrolment, interventions, and assessments is shown in Figure 2. The SPIRIT checklist is provided as Additional file 1.

Statistical analysis and sample size

Descriptive variables will be analysed 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.

A subgroup analysis will be performed according to time of NIV support (primary ventilation or after extubation).

The number of patients to be enrolled is calculated considering clinically relevant a 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.

Quality control and quality assurance procedures

Compliance to protocol

Compliance will be defined as full adherence to protocol. Compliance with the protocol will be ensured by a number of procedures as described.

Site setup

Principal investigators will participate in preparatory meetings in which details on study protocol, non-invasive ventilation, multiparametric polygraph and data collection will be accurately discussed with all NICU staff, including nursing and medical staff.

Safety

Safety endpoints will include incidence, severity, and causality of reported significant adverse events (SAEs). All SAEs will be followed until satisfactory resolution or until the investigator

responsible for the care of the participant deems the event to be chronic or the patient to be stable. All expected and unexpected SAEs, whether or not they are attributable to the study intervention, will be reviewed by the principal investigators to determine if there is a reasonable suspected causal relationship with the intervention. If the relationship is reasonable, SAEs will be reported to the ethics committee and inform all other investigators to guarantee the safety of the participants.

Discussion

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend NIV as the best respiratory support for preterm infants with RDS (1).

It is well known that the NIV is a valid tool to reduce the duration and the need for MV. The reduction in MV is closely related to the development of ventilator lung injury and complications such as BPD. Early switching from the MV to the NIV has been advocated, even for extremely preterm infants (14). Therefore, it is desirable to identify the best type of NIV to be used at birth or after extubation.

The popularity of NIPPV is rising since its comparison to NCPAP has demonstrated significant decrease in respiratory failure, re-intubation rates and extubation failure (6). However, there is insufficient evidence to recommend NIPPV as primary mode of respiratory support in the delivery room (1).

Synchronisation may be important in delivering effective NIPPV: studies using SNIPPV and delivering NIPPV to infants by a ventilator observed benefits more consistently (7).

279 The periodic breaths of NIPPV increase tidal volume leading to enhanced removal of CO2,
280 sustained alveolar ventilation during episodes of apnea and increased functional residual
281 capacity (FRC) (4,15). Asynchronies between ventilator and infant breaths may alter
282 spontaneous breath rhythm, induce glottal narrowing, increase WOB, increase abdominal
283 distension and cause volutrauma. SNIPPV seems to be associated with an increased tidal and
284 minute volumes when compared to NCPAP (16). It has also been demonstrated that SNIPPV
285 recruits collapsed alveoli, thereby increasing FRC and decreasing the need for MV (17). Several
286 explanations may account for the effectiveness of SNIPPV: decreased thoracoabdominal motion
287 asynchrony and flow resistance through the nasal prongs, with improved stability of the chest
288 wall and pulmonary mechanics, increased flow delivery in the upper airway with the addition of
289 a PIP above PEEP (18).
290 Synchronization during nasal ventilation is considered to provide a more efficient respiratory
291 support and synchrony. One of the first studies to demonstrate WOB reduction in preterm
292 infants with the use of SNIPPV was done more than 10 years ago (19). Huang et al. (20)
293 supported these benefits of synchronized ventilation achieved by using a Graseby capsule,
294 showing an improved gas exchange and a decreased respiratory effort.
295 Compared to CPAP and NIPPV, SNIPPV is more effective in reducing desaturation and apnoea;
296 compared to CPAP, SNIPPV reduce risk of BPD, of extubation failure and of severe retinopathy
297 of prematurity (16,21).
298 Gizzi et al. compared the effects of flow-SNIPPV, NIPPV and NCPAP on the rate of desaturations
299 and bradycardias in preterm infants with apnoeic spells (mean gestational age at study 30
300 weeks) (12). A randomised crossover study with three treatment phases was conducted:

patients received the three mode of ventilation for 4 hours each, using a nasal conventional ventilator able to provide synchronisation by a pneumotachograph (Giulia® ventilator; GINEVRI srl, Albano Laziale, Rome, Italy). Flow-SNIPPV has been shown to reduce desaturation and apnea in CPAP infants (12).

SNIPPV may be superior to NIPPV even in patients with RDS, as first intention (soon after birth) or after extubation.

As first intention, flow-SNIPPV combined to surfactant seemed to be a promising strategy for treating infants in the acute phase of RDS (22). However, a recent meta-analysis showed that early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation, without any additional benefits with SNIPPV (10). Recently, Handoka et al. reported grade of RDS, mean airway pressure and antenatal steroid use as the predictors of early SNIPPV failure (18).

A lower WOB is an important consideration when choosing which non-invasive mode should be used to support preterm infants immediately after extubation. SNIPPV and NIPPV delivered by a ventilator demonstrated short-term benefit for extubation failure and long-term pulmonary effects for BPD and pulmonary air leaks (7). SNIPPV post-extubation reduced the WOB and thoracoabdominal asynchrony (5,11).

Several fans are currently available for SNIPPV. The Giulia® ventilator (GINEVRI srl, Albano Laziale, Rome, Italy) is one of them, providing a flow-SNIPPV. The Giulia® uses a pressure sensor. The trigger quality of this system is not known.

It is known that NIPPV produces a percentage of ineffective acts because they are not synchronized with patient's acts. On the other hand, a bad synchronization system could have

the effect of increasing respiratory work. Our hypothesis is that a valid synchronization could reduce the respiratory work and increase the volume per minute exchanged without interfering with the natural respiratory rhythm of the infant with RDS. A randomised crossover study with two treatment phases will be conducted to evaluate short-term effects of SNIPPV vs NIPPV in a group of preterm infants on cardiorespiratory events at their first approach to NIV ventilation as first intention or after extubation.

The results of this study will allow us to evaluate the effectiveness of the synchronization obtained by the flow-SNIPPV.

The results of this study will demonstrate whether synchronization is the most effective ventilation mode even in preterm infants with RDS.

Trial status

The protocol is syncNIPPV17 version no. 1.6. The recruitment is expected to begin on 1 September 2020. The time expected to complete the recruitment is about 31 August 2021.

Abbreviations

BPD: bronchopulmonary dysplasia; Bpm: beats per minute; CPAP: continuous positive airway pressure; flow-SNIPPV: flow-synchronized nasal intermittent positive pressure ventilation; FiO2: fraction of inspired oxygen; FRC: functional residual capacity; GA: gestational age; HR: heart rate; MV: mechanical ventilation; NICU: neonatal intensive care unit; NIPPV: nasal intermittent positive pressure ventilation; NIV: non-invasive ventilation; PEEP: positive end expiratory pressure; PIP: peak inspiratory pressure; RDS: respiratory distress syndrome; RR: respiratory rate;

SatO2 TC: transcutaneous O2 saturation; SNIPPV: synchronized Nasal intermittent positive pressure ventilation; WOB: work of breathing; SAEs: significant adverse events

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Not applicable.

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FCr, FCh and EM conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. SMB, EM, GM and CP reviewed and revised the manuscript and approved the final manuscript as submitted. MF collaborated to design the study and approved the final manuscript as submitted. AC and EB critically reviewed the manuscript and approved the final manuscript as submitted. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Study protocol was approved with the approval number 0077664 on 7 August 2017 by the ethics committee of the neonatal intensive care unit (Comitato Etico Interaziendale – AOU Città della Salute e della Scienza di Torino; phone: + 39.011.6336547; email: comitatoetico@cittadellasalute.to.it). Written, informed consent to participate will be obtained from all participants' parents/legal guardian.

Consent for publication

Not applicable.

Competing interests

Engineer Mattia Ferroglio declares to have a contract with GINEVRI srl as responsible for technical assistance for the Piedmont region. All the other authors declare that they have no competing interests.

Author details

[1]Neonatal Intensive Care Unit, Department of Public Health and Pediatrics, University of Turin, Turin, Italy

[2]Department of Public Health and Pediatric Sciences, Postgraduate School of Pediatrics, University of Turin, Turin, Italy,

References

1. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. Neonatology. 2019;115(4):432–50.
2. Cummings JJ, Polin RA, Committee on Fetus and Newborn, American Academy of Pediatrics. Noninvasive Respiratory Support. Pediatrics. gennaio 2016;137(1).
3. Isayama T, Iwami H, McDonald S, Beyene J. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. JAMA. 9 agosto 2016;316(6):611–24.
4. Owen LS, Manley BJ. Nasal intermittent positive pressure ventilation in preterm infants: Equipment, evidence, and synchronization. Semin Fetal Neonatal Med. giugno 2016;21(3):146–53.
5. Permall DL, Pasha AB, Chen X. Current insights in non-invasive ventilation for the treatment of neonatal respiratory disease. Ital J Pediatr. 19 agosto 2019;45(1):105.
6. Ferguson KN, Roberts CT, Manley BJ, Davis PG. Interventions to Improve Rates of Successful Extubation in Preterm Infants: A Systematic Review and Meta-analysis. JAMA Pediatr. 1 febbraio 2017;171(2):165.
7. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. 2017;
8. Moretti C, Gizzi C, Montecchia F, Barbàra CS, Midulla F, Sanchez-Luna M, et al. Synchronized Nasal Intermittent Positive Pressure Ventilation of the Newborn: Technical Issues and Clinical Results. Neonatology. 3 giugno 2016;109(4):359–65.

9. Mowitz ME, Zupancic J a. F, Millar D, Kirpalani H, Gaulton JS, Roberts RS, et al. Prospective economic evaluation alongside the non-invasive ventilation trial. J Perinatol Off J Calif Perinat Assoc. 2017;37(1):61–6.
10. Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev. 15 2016;12:CD005384.
11. Charles E, Hunt KA, Rafferty GF, Peacock JL, Greenough A. Work of breathing during HHHFNC and synchronised NIPPV following extubation. Eur J Pediatr. gennaio 2019;178(1):105–10.
12. Gizzi C, Montecchia F, Panetta V, Castellano C, Mariani C, Campelli M, et al. Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised cross-over trial. Arch Dis Child - Fetal Neonatal Ed. 2015;100(1):F17–23.
13. Salvo V, Lista G, Lupo E, Ricotti A, Zimmermann LJI, Gavilanes AWD, et al. Noninvasive Ventilation Strategies for Early Treatment of RDS in Preterm Infants: An RCT. PEDIATRICS. 2015;135(3):444–51.
14. Manley BJ, Doyle LW, Owen LS, Davis PG. Extubating Extremely Preterm Infants: Predictors of Success and Outcomes following Failure. J Pediatr. giugno 2016;173:45–9.
15. Alexiou S, Panitch HB. Physiology of non-invasive respiratory support. Semin Fetal Neonatal Med. giugno 2016;21(3):174–80.

16. Moretti C, Giannini L, Fassi C, Gizzi C, Papoff P, Colarizi P. Nasal flow-synchronized intermittent positive pressure ventilation to facilitate weaning in very low-birthweight infants: Unmasked randomized controlled trial. Pediatr Int. 2008;50(1):85–91.
17. Li W, Long C, Zhangxue H, Jinning Z, Shifang T, Juan M, et al. Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: A meta-analysis and up-date. Pediatr Pulmonol. 2015;50(4):402–9.
18. Handoka NM, Azzam M, Gobarah A. Predictors of early synchronized non-invasive ventilation failure for infants < 32 weeks of gestational age with respiratory distress syndrome. Arch Med Sci AMS. maggio 2019;15(3):680–7.
19. Aghai ZH, Saslow JG, Nakhla T, Milcarek B, Hart J, Lawrysh-Plunkett R, et al. Synchronized nasal intermittent positive pressure ventilation (SNIPPV) decreases work of breathing (WOB) in premature infants with respiratory distress syndrome (RDS) compared to nasal continuous positive airway pressure (NCPAP). Pediatr Pulmonol. 2006;41(9):875–81.
20. Huang L, Mendler MR, Waitz M, Schmid M, Hassan MA, Hummler HD. Effects of Synchronization during Noninvasive Intermittent Mandatory Ventilation in Preterm Infants with Respiratory Distress Syndrome Immediately after Extubation. Neonatology. 2015;108(2):108–14.
21. Bhandari V. Noninvasive Respiratory Support in the Preterm Infant. Clin Perinatol. settembre 2012;39(3):497–511.

22. Gizzi C, Papoff P, Giordano I, Massenzi L, Barbàra CS, Campelli M, et al. Flow-Synchronized Nasal Intermittent Positive Pressure Ventilation for Infants <32 Weeks' Gestation with Respiratory Distress Syndrome. Crit Care Res Pract. 2012;2012:1–7.

Figures

Figure 1. Study design

Figure 2. Spirit figure

Tables

Table 1. Data recorded before and during the study period

Before enrolment	**During the study period**
ANAMNESTIC VARIABLES	CARDIO-RESPIRATORY VARIABLES
- GA at birth	- FiO2 to maintain $SatO_2$ TC 90-94% (as weighted mean)
- birth weight	- NIV failure[a] and endotracheal intubation
- delivery type	- Number of cardiorespiratory events[b]
- APGAR at 1/5 minutes (and 10 minutes if available)	OTHER POLYGRAPH VARIABLES (continuous monitoring)
- presence of intrauterine growth restriction	- HR
- maternal administration of magnesium sulphate	- RR
- steroid prenatal prophylaxis (number of doses)	- SatO2 TC
- intrapartum antibiotic prophylaxis (if indicated)	- thoracic impedance
- presence of intraamniotic infection and administration of intrapartum antibiotic therapy	- from ventilator: trigger, pressure, flow
CLINICAL VARIABLES	- pressure in ventilator circuit
- surfactant administration (time and number of doses)	CLINICAL VARIABLES
- type and duration of MV previously administered (if any)	- Neonatal Pain Scale score
- type and duration of NIV previously administered (if any)	LABORATORISTIC VARIABLES
	- EGA values at the end of stabilization phase, Phase A and Phase B

- corrected GA at enrolling - caffeine doses administered (if any)

GA gestational age, *MV* mechanical ventilation, *NIV* non-invasive ventilation, *SatO2 TC* transcutaneous O2 saturation, *HR* heart rate, *RR* respiratory rate

[a]NIV failure criteria: FiO2 > 40%, pH < 7.2, pCO2 > 65mmHg, ≥ 3 episodes of desaturations (SatO2 TC < 80%) per hour, ≥ 3 episodes of apnea (> 20 seconds) and/or bradycardia (HR < 80 bpm) per hour, Silverman score > 6. Necrotizing enterocolitis, bowel perforation, and hemodynamic instability are indications of NIV failure.

[b]Cardiorespiratory events are defined as episodes of apnea lasting more than 20 seconds or over 5 seconds if followed by desaturation or bradycardia and/or episodes of desaturation with blood oxygen saturation below 80% for 4 seconds or more and/or episodes of bradycardia with HR below 80 bpm.

Additional Files

Additional file 1. Ethical approval document (original)

Additional file 2. Ethical approval document (translated)

Additional file 3. SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents.

Figures

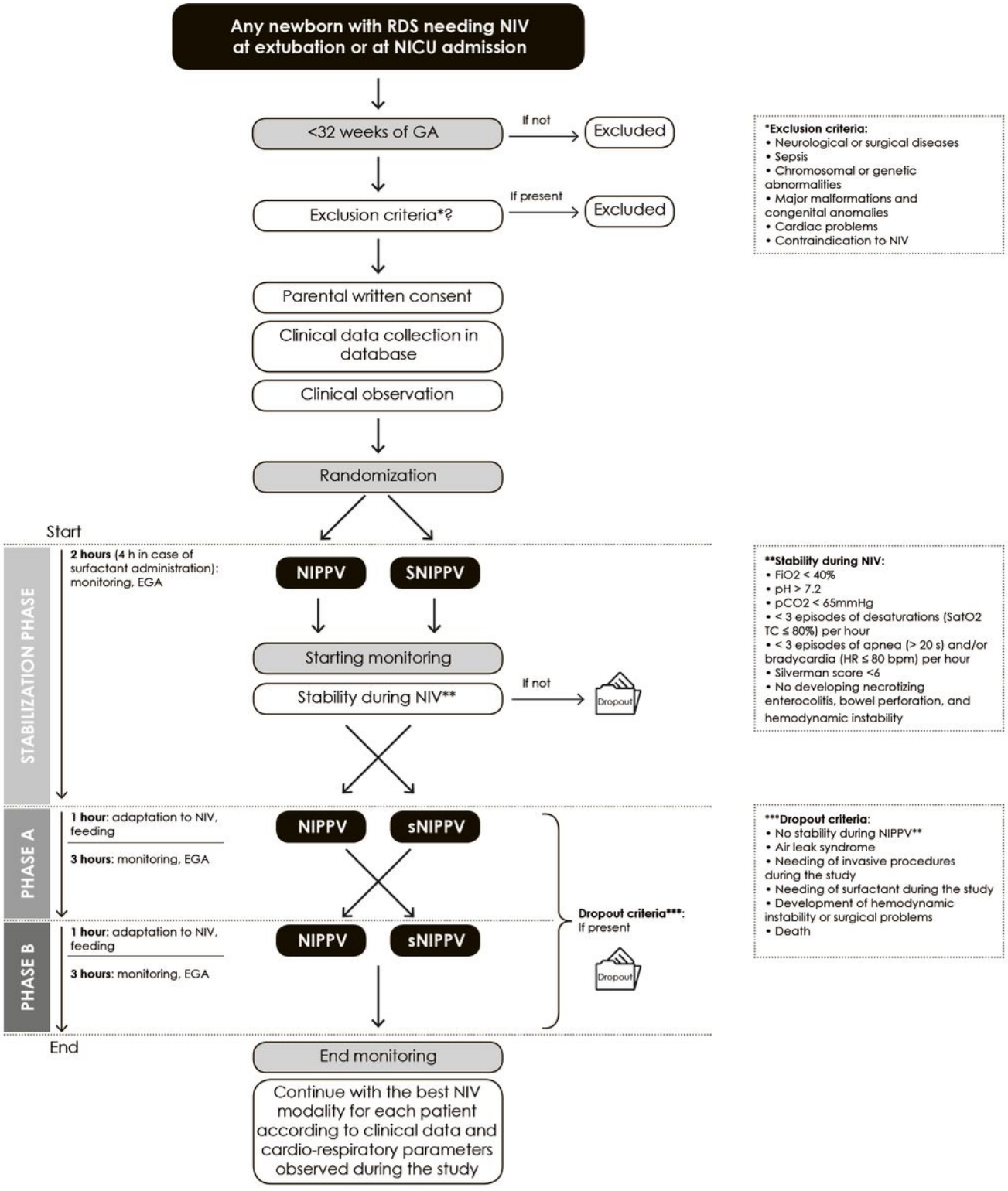
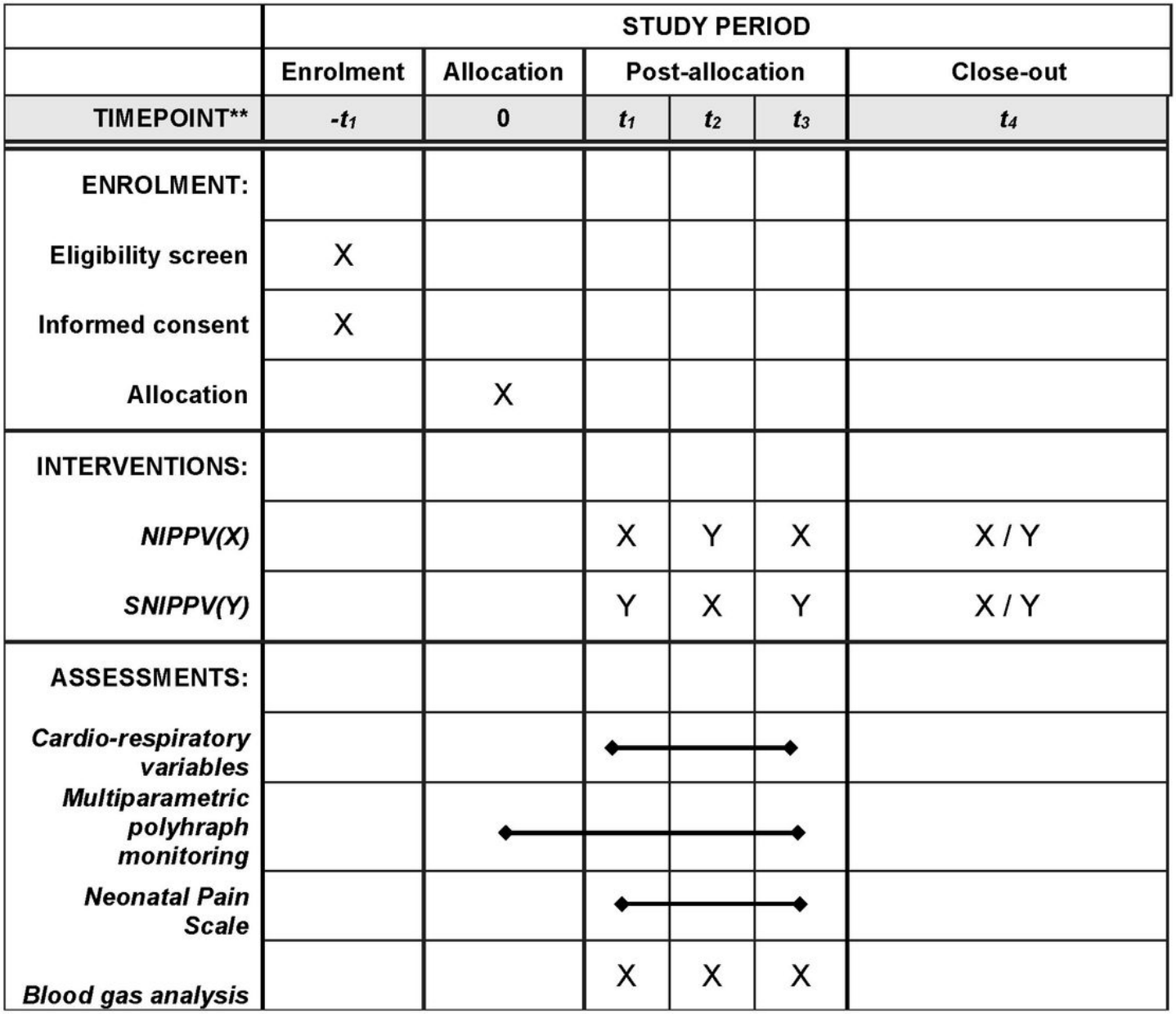


Figure 1

Study design



- t_1: enrolment period: NICU admission or at extubation
- 0: allocation
- t_1: stabilization phase
- t_2: phase A
- t_3: phase B
- t_4: study end

Figure 2

Recommendations for Interventional Trials (SPIRIT), Enrolment, interventions, and assessments

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist.pdf