Ruth
Ruth Rappaport Children's Hospital
Rambam Health Care Campus

This supplement contains the following item:

A translation* of the original and final protocol (no changes done), including statistical analysis methods described in the end of the protocol (page 18).

* The original protocol was not in English.

Study Protocol:

RAM Cannula vs. Binasal Prongs/Mask for Delivering NIPPV in Preterm Infants :Non-Inferiority, Randomized, Controlled Trial

Protocol Version: 1

Funding: None

Principal Investigator: Dr. Ori Hochwald, Rambam medical center, Haifa, Israel

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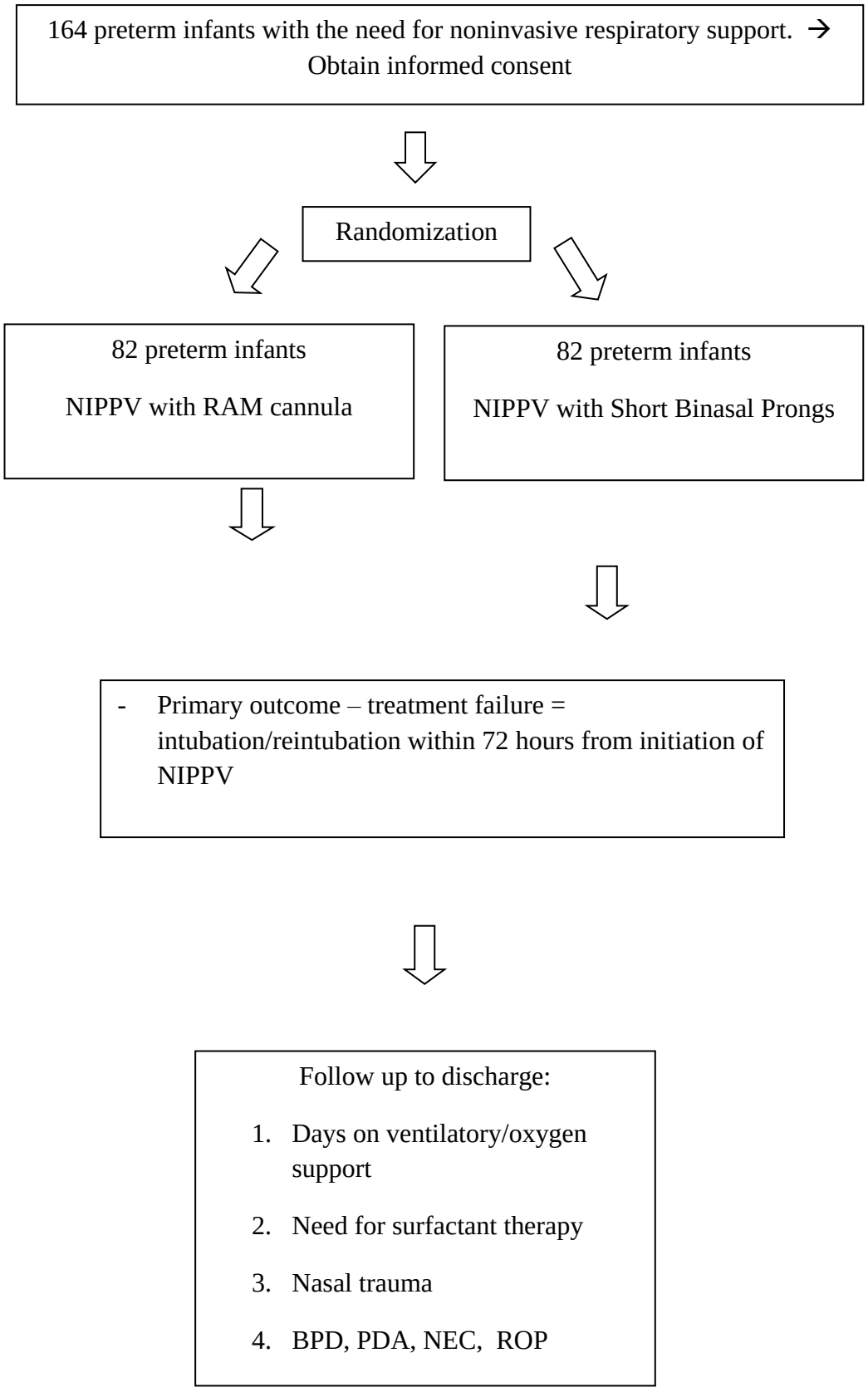
Study summary - flow diagram



1. Synopsis

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Full title	RAM Cannula vs. Binasal Prongs/Mask for Delivering NIPPV in Preterm Infants :Non-Inferiority, Randomized, Controlled Trial
Principal investigator	Dr. Hochwald Ori
Short background	Thanks to ease of use, perceived patient comfort and reduced nasal trauma Ram cannula use has gained increasing popularity and was adopted as default by many NICUs without strong evidence supporting its use. In contrast, there are many other NICUs that completely refrain from using Ram cannula in concern that this long thin interface delivers reduced and suboptimal support. We hypothesized that using Ram cannula would be inferior to short prongs or mask in preterm infants who require noninvasive ventilation for the primary treatment of RDS or post extubation and would result in a higher rate of endotracheal ventilation.
Primary outcome	The need for endotracheal ventilation within 72 hours after initiation of NIPPV, i.e. "Treatment failure".
Secondary outcomes	• Failure between 72 hours and 7 days after initiation of NIPPV • Nasal trauma • The need for surfactant

	• Complications of prematurity (including bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis (bell's staging 2-3), sepsis, intraventricular hemorrhage and periventricular leukomalacia • Air leaks. • Length of invasive and noninvasive respiratory support • Time to full feeds and • Length of hospital stay.
Design	Dual center, randomized, controlled, non-inferiority trial.
Patients	Premature infants born in gestational age between 24^0 and 33^6
Inclusion criteria	Need for noninvasive ventilatory support either • For initial treatment of RDS, or • Post first extubation after birth. Written informed consent. Antepartum consent should be sought when possible, otherwise parents can consent at the earliest opportunity within 4 hours after NIPPV is initiated.
Exclusion criteria	Significant morbidity apart from RDS including: • Cardiac disease (not including patent ductus

	arteriosus) • Congenital malformation • Cardiovascular or respiratory instability because of sepsis, anemia or severe intra-ventricular hemorrhage. Written consent not provided within 4 hours from NIPPV initiation
Devices (type of cannula)	- Ram (Neotech, Valencia, CA) - Short binasal prongs - including the currently used devices in the two units participating in the study: • (INCA Nasal Cannula [CooperSurgical, Inc, Trumbull, CT] or • EasyFlow prongs or mask [Fritz Stephan GmbH]).
Number of patients required	164, 82 in each group
Recruiting centers	Rambam medical center, Haifa, Israel Bnai Zion medical center, Haifa, Israel
Non inferiority analysis	We prespecified a noninferiority margin for Ram cannula of 15% above the failure (intubation within 72 hours) rate for short prongs or mask. Using Ram cannula will be considered noninferior to using SPM if the upper limit of the two-sided 95% confidence interval is less than 15% and the lower limit of the 95% confidence interval is below zero.

Funding	None
Conflict of interest	None
Trial Registration	Clinicaltrials.gov: NCT03081611 (https://clinicaltrials.gov/ct2/show/NCT03081611)

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2. Introduction

In the recent years, in an effort to avoid endotracheal intubation and invasive mechanical ventilation, there has been an increase in the use of noninvasive ventilation in very low birth (VLBW) preterm infants as the initial respiratory support after birth or after extubation [1,2].

Different interfaces are available for applying noninvasive ventilation. The commonly used interfaces include short binasal prongs, nasal masks and Ram cannula. The different properties of these interfaces may affect the pressure and volume transmission, which may have influence on clinical outcomes [3].

The most commonly used interfaces, the standard short binasal prongs and masks, are located at the end of normal caliber ventilator tubing. Unfortunately, short nasal prongs and masks are occasionally associated with discomfort and pressure-related nasal injury [4]. The Ram cannula is made of softer material with a long and narrow tubing for transmitting the pressure to thin walled prongs. This results in a perceived ease of use, comfort and less nasal trauma [5]. However, there is concern that this long thin interface delivers reduced and suboptimal pressure and support compared with the short nasal prongs and masks [6–8]. Despite its widespread use [9], the clinical efficacy of the Ram cannula was not thoroughly studied. To adopt this method for clinical

practice in preterm infants it has to be shown to be non-inferior to binasal prongs/mask interfaces.

The most important factor in noninvasive ventilation of premature infants is supporting the functional residual capacity (FRC) with continuous positive airway pressure (CPAP). This might be the reason for the advantage of NCPAP over HFNC in these infants [10,11]. While both NCPAP and NIPPV support the FRC with NCPAP, different studies showed NIPPV to be either as good as or superior to NCPAP [12,13]. Thus, we will use in this our study the NIPPV as a preferred mode, and evaluate the two interfaces using it.

There are a limited number of studies assessing Ram cannula efficacy in delivering noninvasive ventilation, most of them are bench testing using lung models or focused on measurements of the applied pressures. Those studies used the manufacturer recommendation for prong occlusion of 60–80% of the nares space [6]. Gerdes et al measured mean airway pressure (MAP) delivered through the Ram Cannula as a function of percent nares occlusion in a simulated lung model. With 60–80% nares occlusion, overall delivered MAPs were around 60% of the set CPAP levels. With 100% occlusion the MAPs were within ±0.5 cmH_2O of the set CPAP levels [7]. In summary, studies suggest that using Ram cannula would be potentially more efficacious once lower leak around the cannula and higher ventilatory set pressures are used [3,6–8]. We

found no published randomized controlled trial that compared NIPPV using Ram cannula and short nasal prongs for the initial treatment of RDS.

Compared to short prongs, the RAM cannula is made of softer material and is less cumbersome, resulting in a perceived more comfort and less nasal trauma [5]. In their study on noninvasive ventilation, Nzegwu et al had 17.9% of nasal breakdown using short prongs. In case of nasal breakdown they switched to Ram cannula, and showed no new instances of nasal breakdown or injury with its use [5].

We hypothesized that because of its long thin design, using Ram cannula would be inferior to binasal prongs/mask in preterm infants who require nasal support and would result in a higher rate of endotracheal ventilation.

In this randomized, controlled, non-inferiority study, we aim to compare the ability to prevent intubation in preterm infants in need for ventilatory support for the initial treatment of RDS or post extubation by using nasal intermittent positive pressure ventilation (NIPPV) with either Ram cannula or short binasal prongs/mask (SPM) interfaces.

3. Methods

3.1 Design

Randomized prospective, open, controlled, non-inferiority dual-center study was conducted in the tertiary neonatal intensive care units of Rambam Medical Center and Bnai Zion Medical Center in Haifa, Israel.

Blinding of the intervention is impossible in this study.

3.2 Ethics

This trial was approved by the local ethics committee and was entered to ClinicalTrials.gov database, registration number NCT03081611.

3.3 Subjects

premature infants born in gestational age between 24^0 and 33^6 weeks as assessed by the obstetrical team from dating of last menstrual period or ultrasound

3.4 Subgroups: The study population is divided into two groups:

- The initial-treatment group - infants that needs noninvasive ventilation during the first 7 days of life without prior invasive ventilation in the NICU.
- The post-extubation group includes infants that needed noninvasive ventilation during the first 28 days of life after any period of endotracheal ventilation in the NICU. The latter group will includ infants from the initial-treatment group that are ventilated after the initial treatment with NIPPV. These infants will keep the same interface according to the initial allocation.

3.5 Inclusion criteria

1. Need for noninvasive ventilatory support:
    - For initial treatment all including:
        - Clinical RDS including tachypnea, apneic episodes, grunting and/or retractions
        - Need for more than "low flow" (≤2 lpm) for keeping saturation >90% and/or pCO_2≤60 mmHg.
        - The decision on the need for ventilatory support will be assessed by the attending clinician.
    - Post first extubation after birth – all infants will be treated with NIPPV.

2. Both parents of all participating infants will provide written informed consent. Antepartum consent will be sought when possible. If antepartum consent is not sought, parents will be approached and ask for consent at the earliest opportunity within 4 hours after NIPPV is initiated.

3.6 Exclusion criteria

1. Significant morbidity apart from RDS including:
   - Cardiac disease (not including patent ductus arteriosus)
   - Congenital malformation
   - Cardiovascular or respiratory instability because of sepsis, anemia or severe intra-ventricular hemorrhage.
2. Written consent not provided within 4 hours from NIPPV initiation.

3.7 Randomization

Pre-randomization stratification will be done by groups (initial-treatment and post-extubation) and by BW (< 1250 gr and ≥ 1250 gr) in each study center, separately. Multiple births will be randomized individually. The randomization sequence is computer generated with block size of 4. A note with the type of the assigned interfaces (Ram cannula or short prongs/mask) will be provided in consecutively numbered, opaque envelopes.

3.8 Interventions

Endotracheal intubation criteria in the delivery room are [14]:

- Heart rate ≤100 beats/min despite after noninvasive positive pressure applied
- Insufficient spontaneous respiratory
- Marked and increasing dyspnea.

Early nasal respiratory support with NIPPV will be initiated in any spontaneous breathing premature infant meeting the inclusion criteria.

Exogenous surfactant (200 mg/kg for the 1st dose, 100 mg/kg for the 2nd dose, 1 to 2 doses as needed, Curosurf; Chiesi Farmaceutici, Parma, Italy) will be given only as rescue therapy.

Study intervention

Eligible infants will be randomly assigned to NIPPV with either Ram Cannula (Neotech, Valencia, CA) or short binasal prongs (INCA Nasal Cannula [CooperSurgical, Inc, Trumbull, CT] or EasyFlow prongs [Fritz Stephan GmbH]). The study protocol allows use of EasyFlow mask (Fritz Stephan GmbH) or alternating between short prongs and mask in cases of nasal trauma or for prevention of nasal trauma per unit protocol. Both prongs and mask are referred to as short prongs/mask interface (SPM) for the study purposes. No cross over between Ram cannula and short prongs/mask allowed in the study.

The Ram Canula prongs size will be selected so it will fill approximately 80% of nares. The short prongs size will be selected as per the manufacturer's instructions so it will fill close to 100% of nares without causing local pressure. If used, the mask size will be chosen as per the manufacturer's instructions.

The study team is encouraged to obtain an antepartum consent. If not approached before NIPPV is initiated, NIPPV will be initiated with Ram cannula, and once parents gave their consent, treatment will continue with an

interface according to randomization allocation. Parents will be approached and ask for consent at the earliest opportunity within 4 hours after NIPPV is initiated.

NIPPV will be administered using Leoni (Heinen&Löwenstein, Bad Ems, Germany) or SLE 5000 (SLE, Croydon, UK) ventilators on SIMV mode. The ventilators will be managed by the attending neonatologist according to the following initial and weaning approach.

- Initial NIPPV settings:
    - Peak inspiratory pressure (PIP) of 14-18 cmH_2O (according to chest excursion)
    - Positive end expiratory pressure (PEEP) of 6 cmH_2O
    - Respiratory rate (RR) of 10-30 breaths per minute (BPM)
    - Inspiratory time (Ti) of 0.3-0.35 seconds
    - Saturation targets were 90-94%.
- Settings limits allowed are
    - PIP of 10-24 cmH_2O
    - PEEP of 5-7 cmH_2O
    - RR of 8-40 BPM
- Weaning from NIPPV to no support or to low flow (i.e. ≤2 LPM) will be considered if:

- There was clinical improvement and
- Fraction of inspired oxygen of 0.3 or lower
- PIP ≤16 cmH_2O
- PEEP ≤6 cmH_2O
- RR ≤20 BPM.

All infants will be evaluated at least daily.

Infants with GA<32 will receive caffeine for apnea prevention starting in the 1st day of life. Apneic infants with GA≥32 will receive caffeine as per the attending clinician's discretion.

Surfactant administration using either MIST or INSURE techniques or after intubation according to clinician's discretion and according to the unit protocol.

Using high flow nasal canulla (HFNC) will be done only in cases of significant nasal trauma during NIPPV.

Other aspects of neonatal care will be provided according to the routine unit protocols.

3.9 Outcomes

The primary outcome: Treatment failure within 72 hours after initiation of NIPPV, i.e. the need for endotracheal ventilation.

- intubation and ventilated criteria: clinical deterioration (increased respiratory distress) accompanied by at least one of the following or worsening of the following:
    - pH<7.20 and pCO2> 60 mm Hg
    - Oxygen saturation by pulse-oximetry (SpO2)<90% on FiO2>50%,
    - Recurrent significant apnea requiring repeated stimulation or bag-and-mask ventilation despite the use of caffeine and excluding technical problems
    - All of the above despite allowing setting on NIPPV up to PIP=24 cmH_2O, PEEP= 7 cmH_2O and RR of 40.
- Moderate to severe nasal trauma within 72 hours, requiring change of interface will be also considered as a failure criterion.
- Surfactant administration via the INSURE technique (intubation-surfactant-extubation immediately after surfactant administration) or

the MIST (minimally invasive surfactant therapy) via a thin catheter will not considered a failure of the NIPPV treatment.

Secondary outcomes included:

- Treatment failure between 72 hours and 7 days after initiation of NIPPV.
- The reason for treatment failure
- Nasal trauma: graded as mild- persistent erythema, moderate- superficial ulceration and severe- necrosis.
- The need for surfactant
- Complications of prematurity including:
    - Bronchopulmonary dysplasia - defined as the need for oxygen therapy or positive pressure (CPAP or NIPPV) or high flow nasal cannula of >2LPM at 36 weeks gestation
    - Patent ductus arteriosus – diagnosed by echocardiography by cardiologist,
    - Necrotizing enterocolitis, bell's staging 2-3 – diagnosed by clinical signs and x-ray reviewed by pediatric radiologist
    - Culture proven sepsis

- Intraventricular hemorrhage (any grade and grades 3-4) and/or periventricular leukomalacia diagnosed by cranial ultrasound reviewed by pediatric radiologist. Routine ultrasound schedule will be 3, 14 and 28 days and before discharge if older than 60 days at discharge.

- Complications related to ventilation (i.e. air leaks).
- Length of invasive and noninvasive respiratory support.
- Time to "full feeds", i.e 140 ml/k/day.
- Length of hospital stay.

All data will be entered to computerized CRF.

3.10 Safety

All adverse events will be reported to the ethical committee and to the principal investigator (Dr. Ori Hochwald) according to the rules of Good Clinical Practice (GCP). Definitions:

Adverse event (AE)

Any harmful event occurring in a person who is engaged in biomedical research, whether or not it is related to the research or the product to which the research relates.

Adverse reaction to a medical device (MD)

Any harmful and unwanted reaction to a medical device or any incident that could have caused such a reaction if an appropriate action had not been taken, in a person who is engaged for research or in the user of the medical device or any effect related to a failure or alteration of an in vitro diagnostic medical device that is harmful to the health of a person who is suitable for research.

Serious event or adverse reaction

Any adverse event or reaction that results in death, endangers the life of the person

undergoing research, requires hospitalization or prolongation of hospitalization, causes significant or lasting disability or handicap, or results in a congenital anomaly or malformation, and in the case of the drug, at any dose administered.

Unexpected adverse reaction for research involving a medical device

Any adverse reaction whose nature, severity or course does not correspond to the information contained in the instructions or instructions for use when the medical device is CE marked, and in the investigator's brochure when it is not so marked.

3.11 Ethical Aspect

Parents of children will be informed in full and fair manner, in understandable terms, of the objectives and constraints of the research, the possible risks involved, the necessary surveillance and safety measures, their rights to refuse to participate in the research or the possibility of withdrawing at any time. All this information is contained in an information and consent form given to the parents.

In order to ensure medical confidentiality and data protection, written consent forms and un-named clinical data will be retained by the investigator for a period of fifteen years after the end of the trial. All trial data will be computerized and kept confidential. As patients' names are kept secret, documentation and clinical data will be identified only by study number.

The data will be entered to computerized CRF.

No funding or conflict of interest are present in this study.

4. ***Statistical Analysis***

The statistical analysis will be carried out by prof. A Riskin and hi statistical team (Bnai Zion medical center Haifa, Israel).

The statistical analysis will be carried out with "intention to treat", i.e the intervention considered in the analysis will be the one resulting from randomization.

Based on our units' previous data we estimate that treatment failure within 72 hours after NIPPV initiation would be ~ 18% using short prongs/mask (SPM). We prespecified a noninferiority margin for Ram cannula of 15% above the failure (intubation within 72 hours) rate for short prongs or mask. This was considered clinically significant and based on previous studied. [11,15] Using Ram cannula will be considered noninferior to using SPM if the upper limit of the two-sided 90% confidence interval is less than 15% and the lower limit of the 90% confidence interval was below zero [16].

Using Significance level (p value) of 5% and 80% power, a sample of 164 infants is required. The calculation done by power calculator for binary outcome noninferiority trial. Available from: https://www.sealedenvelope.com/power/binary-noninferior/ [Accessed Mon Oct 24 2016]. We aim to include 85-90 infants in each arm in case of losts to follow up.

The variables will be summarized by their mean (standard deviation), median (range) or percentage depending on the type of variable.

For comparing the binomial proportions in failure rate for non-inferiority based on the score test of Farrington and Manning (1990) we will use SAS 9.4 statistical software with non-inferiority margin of 0.15. We will also compare failure rate (primary outcome) using Chi square analysis. Although theoretically not needed for non-inferiority description, Chi-square is more often used by clinicians and probably therefore it was mentioned in previously published non-inferiority trials. [10]

Chi-square test will be used to compare dichotomous variables. Student's t-test and Mann–Whitney U test will be used for normal and abnormal distribution, respectively, to compare continuous variables. We will use Shapiro-Wilks test to assess normal distribution of the results. Analyses were performed Using SPSS for Windows v. 19.0 (SPSS Inc, Chicago, IL). A p-value of < 0.05will be considered statistically significant.

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