Research Protocol (Full Proposal)
Human Research Ethics Committee (HREC)
Faculty of Medicine, Prince of Songkla University

NCT04323397, Date 15 October 2019

1. Title of the study

Nasal High Frequency Oscillatory versus Synchronized Intermittent Positive Pressure Ventilation in Neonate following Extubation: Randomized Controlled Crossover Study

2. Principal Investigator

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3. Sub-investigators and advisors

Name	Position/Affiliation	E-mail address and phone number	Responsibility in the project
1. Kulthida Baingam	Pediatric resident/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	Kulthida.b93@gmail.com +66 869559933	designed the data collection instruments, collected data, performed the initial analyses, drafted the initial manuscript (MS) and revised the MS.
2. Manapat Phatigomet	Neonatal fellow/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	manapatpang@gmail.com +66 869564774	designed the data collection instruments, collected data, performed the initial analyses, drafted the initial MS and revised the MS.
3. Gunlawadee Maneenil	Assistant professor/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	kookwadee@hotmail.com +66 980169491	conceptualized the study, coordinated, supervised data collection, critically reviewed the manuscript, and approved the final MS

Name	Position/Affiliation	E-mail address and phone number	Responsibility in the project
4. Supaporn Dissaneevate	Assistant professor/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	dsupapor@medicine.psu.ac.th +66 817887765	conceptualized the study, coordinated, supervised data collection, critically reviewed the manuscript, and approved the final MS
5. Waricha Janjindamai	Associate professor/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	jwaricha@medicine.psu.ac.th +66 816788116	conceptualized the study, coordinated, supervised data collection, critically reviewed the manuscript, and approved the final MS
6. Sireepatch Cheamsanit	Neonatal fellow/ Department of Pediatrics, Faculty of Medicine, Prince of Songkla University	happiipc@gmail.com +66 846214237	coordinated intervention

4. Student support

Check ✓ in ( ) that apply

( ) Not associated

(✓) Undergrad./post grad. (indicate resident, fellow, master, PhD student)

5. Keywords:

High-Frequency Ventilation, Intermittent Positive-Pressure Ventilation, Newborn, Noninvasive Ventilation

6. Background and rationale

Non-invasive ventilation (NIV) in neonate has 4 main modes

1. Nasal continuous positive airway pressure (nCPAP)
2. Nasal biphasic CPAP (nBi-CPAP)
3. Nasal intermittent positive pressure ventilation (nIPPV) or nasal synchronized IPPV (nSIPPV)
4. Nasal high frequency oscillation (nHFO)

From meta-analyses, respiratory and extubation failure in n(S)IPPV and nHFO modes were lower than nCPAP. However, most studies were enrolled by primary support but few studies from post-extubation and high-heterogeneity.

Knowledge gap

The comparison of n(S)IPPV and nHFO is still limited in neonatal period. In ClinicalTrial.gov, there are 3 registry studies in Table 1.

Table 1 The studies were registered in ClinicalTrial.gov

U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Saved Studies

Saved Studies (3)

Saved Studies

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☑	Recruiting	Nasal High-frequency Jet Ventilation (nHFJV) Following Extubation in Preterm Infants	• Infant,Premature • Respiratory Failure • Respiratory Insufficiency • Respiratory Distress Syndrome in Premature Infant	• Other: Nasal high-frequency jet ventilation (nHFJV) • Other: Nasal intermittent positive pressure ventilation (NIPPV)	• University of Utah Salt Lake City, Utah, United States • Primary Children's Hospital Salt Lake City, Utah, United States
2	☑	Recruiting	A Trial Comparing Noninvasive Ventilation Strategies in Preterm Infants Following Extubation	• Intubated Infants Were Intend to Extubation Using Noninvasive Ventilation Strategies	• Device: NHFOV • Device: NCPAP • Device: NIPPV	• Daping Hospital and the Research Institute of Surgery of the Third Military Medical University Chongqing, Chongqing, China
3	☑	Unknown †	Nasal High Frequency Oscillatory Versus Nasal Intermittent Positive Pressure Ventilation in Neonate After Extubation	• Respiratory Insufficiency	• Device: NIPPV • Device: NHFOV	

† Study has passed its completion date and status has not been verified in more than two years.

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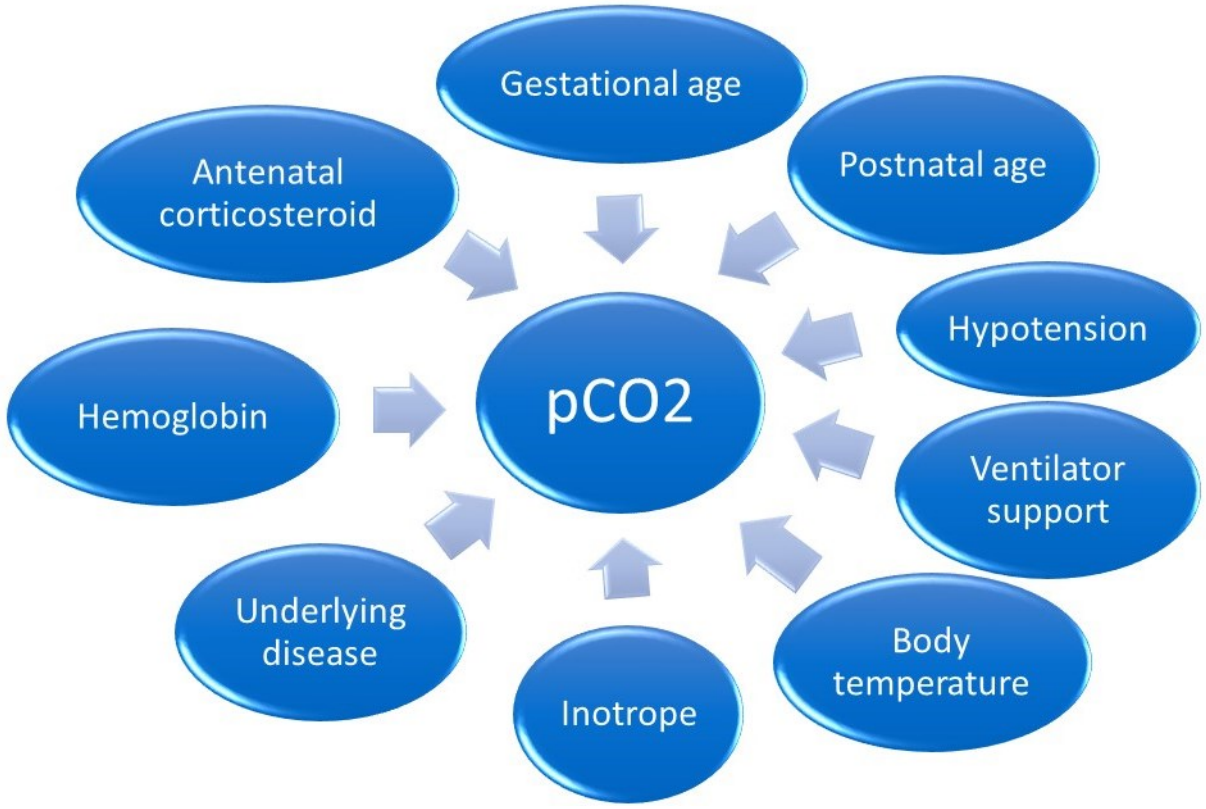
For Patients and Families | For Researchers | For Study Record Managers

7. Objective(s) of the study

Primary objective: To assess the pCO_2 after 2 hours of nHFO compared with 2 hours of nSIPPV in crossover study.

Secondary objective: To assess the reintubation rate within 7 days between non-invasive ventilations (nHFO vs nSIPPV) from the latter NIV mode in parallel study

8. Study flow diagram and/or Conceptual framework



9. Literature review

Mechanical ventilation was introduced to treat respiratory failure in preterm infants or sick neonates then improvements in survival.[1,2] However, the complications from short or long term use of ventilation can result in unintended harm or burden (e.g., air leak syndrome, pneumonia, bronchopulmonary dysplasia, neurological injury, retinopathy of prematurity).[3,4] To reduce these risks, clinicians should aggressive extubated neonates as early as possible. Respiratory (focus on blood gas as well as partial pressure CO_2 [pCO_2]) or extubation (focus on clinical condition as well as reintubation) failure was worrisome in pediatrician and parents if the neonate was reintubated owing to complete recovery of lung disease or inadequate respiratory drive.

Non-invasive ventilation (NIV) was supported for primary respiratory support (initial mode before endotracheal intubation) or post-extubation. Nasal continuous positive airway pressure (nCPAP) was familiar to NIV mode in neonatal respiratory support. Nowadays, the new NIV modalities are nasal intermittent synchronized positive pressure ventilation (nSIPPV) and nasal high frequency oscillation (nHFO).

To increase the likelihood of nCPAP success, other new modalities of NIV may be interesting. From theory, nSIPPV and nHFO combines peak inspiratory pressure (PIP) with synchrony and high-frequency oscillations without synchrony above CPAP, respectively. From meta-analysis, nSIPPV and nHFO were statistically significant superior than nCPAP both respiratory and extubation failure in neonate (**Table 2, Fig. 2-5**).[5,6]

The aim of our study was to investigate the efficacy of nHFOV and nSIPPV for CO_2 clearance and reintubation rate after extubated neonates. We hypothesized that nHFOV mode would improve CO_2 clearance better than nSIPPV mode.

Table 2 Meta-analyses compared nIPPV, nSIPPV, nBi-CPAP, and nHFO to nCPAP

Intervention	Control		Respiratory failure	Reintubation within 7 days
Interventions to improve rates of successful extubation in preterm infants: a systematic review and meta-analysis. JAMA Pediatr 2017;171:165-74.				
n(S)IPPV or nBi-CPAP	nCPAP	RR (95%CI)	.70 (.60, .81)	.74 (.64, .85)
• 9 RCTs (Fig. 1-2)		RD (95%CI)	-.13 (-.18, -.08)	-.10 (-.15, -.05)
		NNT (95%CI)	8 (5-13)	10 (6-20)
		I^2	66%	51%
nSIPPV	nCPAP	RR (95%CI)	.25 (.15, .41)	
• 5 RCTs (Fig. 1)		RD (95%CI)	-.33 (-.43, -.23)	
		NNT (95%CI)	4 (2-5)	
		I^2	0%	
Noninvasive high-frequency oscillatory ventilation as respiratory support in preterm infants: a meta-analysis of randomized controlled trials. Respir Res 2019;20:58.				
nHFO	nBi-CPAP or nCPAP			
• 5 RCTs (1 postextubation, 4 primary support)		pCO_2, WMD 95%CI), I^2	-4.61 (-7.94, -1.28), 67%	
		ΔpCO_2, WMD 95%CI), I^2	-4.89 (-8.36, -1.42), 70%	
• 7 RCTs (1 postextubation, 6 primary support)		RR (95%CI), I^2		.50 (.36, .70), 0%

eFigure 1. NIPPV vs. CPAP: Respiratory failure; subgroup analysis by method of NIPPV

Study or Subgroup	NIPPV Events	NIPPV Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Synchronized						
Gao 2010	6	25	15	25	5.2%	0.40 [0.19, 0.86]
Moretti 2008	2	32	12	31	4.3%	0.16 [0.04, 0.66]
Barrington 2001	4	27	12	27	4.2%	0.33 [0.12, 0.90]
Khalaf 2001	2	34	12	30	4.5%	0.15 [0.04, 0.60]
Friedlich 1999	1	22	7	19	2.6%	0.12 [0.02, 0.91]
Subtotal (95% CI)		**140**		132	**20.8%**	**0.25 [0.15, 0.41]**
Total events	15		58			
Heterogeneity: $Chi^2 = 3.17$, df = 4 (P = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 5.40 (P < 0.00001)						
3.1.2 Non-synchronized						
Kahramaner 2013	5	39	10	28	4.1%	0.36 [0.14, 0.94]
O'Brien 2012	22	67	29	69	10.0%	0.78 [0.50, 1.21]
Khorana 2009	2	24	4	24	1.4%	0.50 [0.10, 2.48]
Subtotal (95% CI)		**130**		121	**15.5%**	**0.64 [0.44, 0.95]**
Total events	29		43			
Heterogeneity: $Chi^2 = 2.26$, df = 2 (P = 0.32); $I^2 = 12\%$						
Test for overall effect: Z = 2.22 (P = 0.03)						
3.1.3 Mixed						
Kirpalani 2013	156	423	182	422	63.7%	0.86 [0.72, 1.01]
Subtotal (95% CI)		**423**		422	**63.7%**	**0.86 [0.72, 1.01]**
Total events	156		182			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
Total (95% CI)		**693**		675	**100.0%**	**0.70 [0.60, 0.81]**
Total events	200		283			
Heterogeneity: $Chi^2 = 23.87$, df = 8 (P = 0.002); $I^2 = 66\%$						
Test for overall effect: Z = 4.89 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 21.30$, df = 2 (P < 0.0001), $I^2 = 90.6\%$						

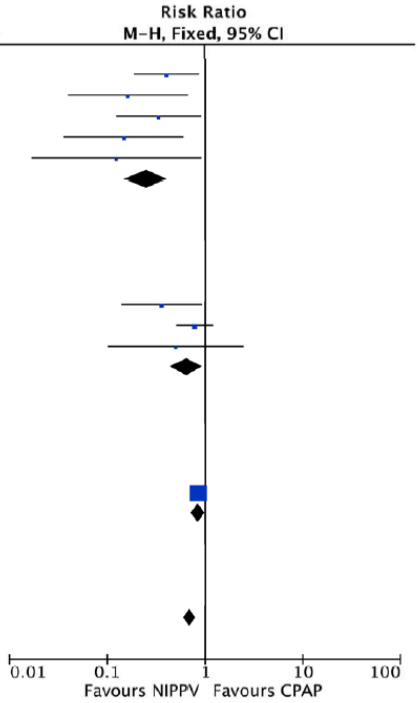
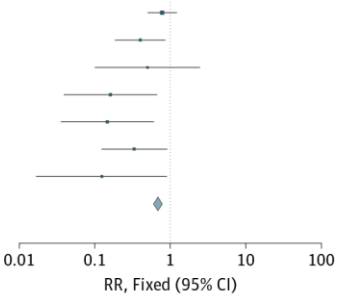


Fig. 2 Respiratory failure compared nSIPPV, nIPPV, mixed modes to nCPAP

A Respiratory failure

Study or Subgroup	NIPPV No. of Events	NIPPV Total No.	NCPAP No. of Events	NCPAP Total No.	RR M-H, Fixed (95% CI)	Weight, %
Kirpalani et al,[31] 2013	156	423	182	422	0.86 (0.72-1.01)	63.7
Kahramaner et al,[32] 2013	5	39	10	28	0.36 (0.14-0.94)	4.1
O'Brien et al,[33] 2012	22	67	29	69	0.78 (0.50-1.21)	10.0
Gao et al,[34] 2010	6	25	15	25	0.40 (0.19-0.86)	5.2
Khorana et al,[35] 2009	2	24	4	24	0.50 (0.10-2.48)	1.4
Moretti et al,[36] 2008	2	32	12	31	0.16 (0.04-0.66)	4.3
Khalaf et al,[37] 2001	2	34	12	30	0.15 (0.04-0.60)	4.5
Barrington et al,[38] 2001	4	27	12	27	0.33 (0.12-0.90)	4.2
Friedlich et al,[39] 1999	1	22	7	19	0.12 (0.02-0.91)	2.6
Total (95% CI)		**693**		**675**	**0.70 (0.60-0.81)**	**100.0**
Total events	200		283			
Heterogeneity: $\chi^2 = 23.87$, $df = 8$ ($P = .002$); $I^2 = 66\%$						
Test for overall effect: $z = 4.89$ ($P < .001$)						



B Reintubation

Study or Subgroup	NIPPV No. of Events	NIPPV Total No.	NCPAP No. of Events	NCPAP Total No.	RR M-H, Fixed (95% CI)	Weight, %
Kahramener et al,[32] 2013	5	39	10	28	0.36 (0.14-0.94)	4.3
Kirpalani et al,[31] 2013	156	423	182	422	0.86 (0.72-1.01)	67.9
O'Brien et al,[33] 2012	22	67	29	69	0.78 (0.50-1.21)	10.6
Gao et al,[34] 2010	6	25	15	25	0.40 (0.19-0.86)	5.6
Khorana et al,[35] 2009	2	24	4	24	0.50 (0.10-2.48)	1.5
Moretti et al,[36] 2008	2	32	12	31	0.16 (0.04-0.66)	4.5
Khalaf et al,[37] 2001	2	34	10	30	0.18 (0.04-0.74)	4.0
Barrington et al,[38] 2001	3	27	3	27	1.00 (0.22-4.52)	1.1
Friedlich et al,[39] 1999	1	22	1	19	0.86 (0.06-12.89)	0.4
Total (95% CI)		**693**		**675**	**0.74 (0.64-0.85)**	**100.0**
Total events	199		266			
Heterogeneity: $\chi^2 = 16.36$, $df = 8$ ($P = .04$); $I^2 = 51\%$						
Test for overall effect: $z = 4.06$ ($P < .001$)						

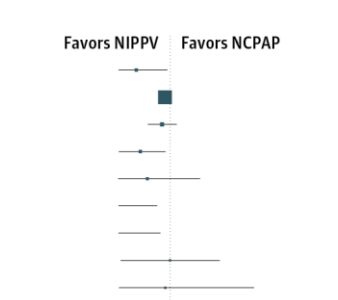


Fig. 3 Respiratory failure and reintubation compared n(S)IPPV to nCPAP

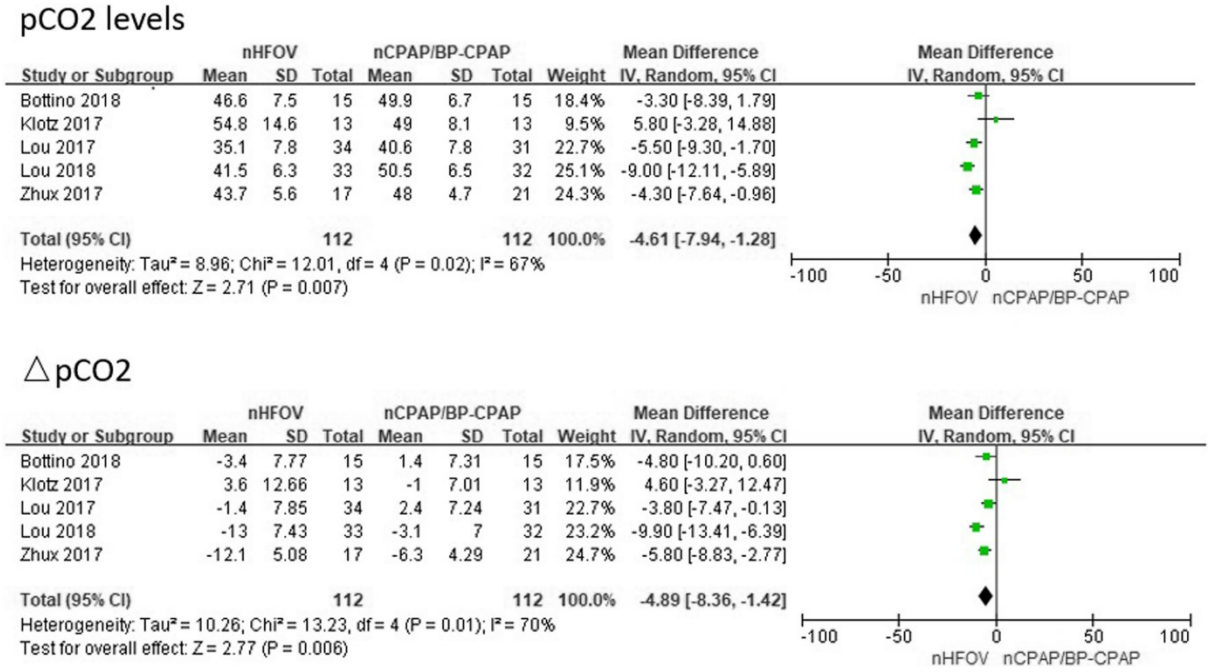


Fig. 4 pCO_2 and ΔpCO_2 between nHFO and nBi-CPAP or nCPAP

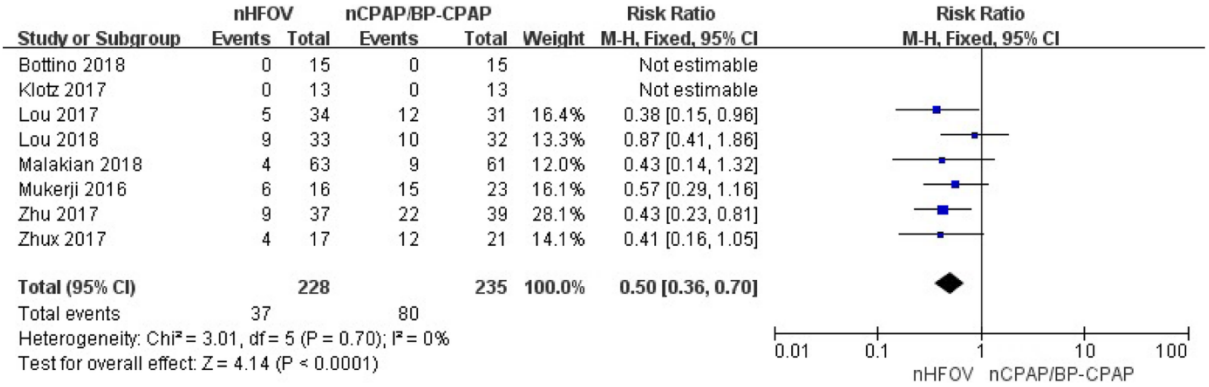


Fig. 5 Intubation between nHFO and nBi-CPAP or nCPAP

10. Research methodology

10.1. Study design: Non-blinded prospective (pragmatic) randomized controlled cross-over study

10.2. Setting of the study/Trial site: Neonatal Intensive Care Unit (NICU), Songklanagarind Hospital

10.3. Target population: NICU admitted neonate

10.4. Study population: Ventilated neonate

10.5. Inclusion criteria

1. Born in hospital and admit in NICU
2. The first endotracheal intubation and need NIV if extubation
3. Neonate has not been intervened from another RCT study

10.6. Exclusion criteria

1. Major congenital anomalies or chromosomal abnormalities
2. Neuromuscular diseases
3. Upper respiratory tract abnormalities
4. Suspected congenital lung diseases or pulmonary hypoplasia
5. Need for surgery known before the first extubation
6. Grade IV intraventricular hemorrhage (IVH) occurring before the first extubation
7. Palliative care
8. Unplanned extubation
9. Parents' decision not to participate

10.7. Participant withdrawal criteria

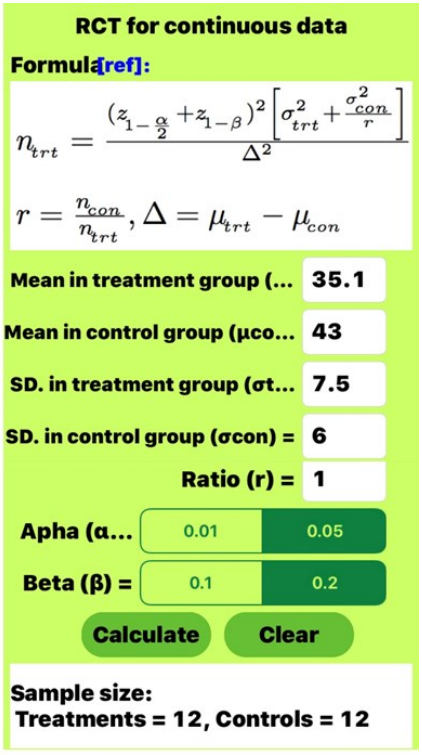
1. Parents' decision not to participate
2. Reintubation during 4-hour cross-over study

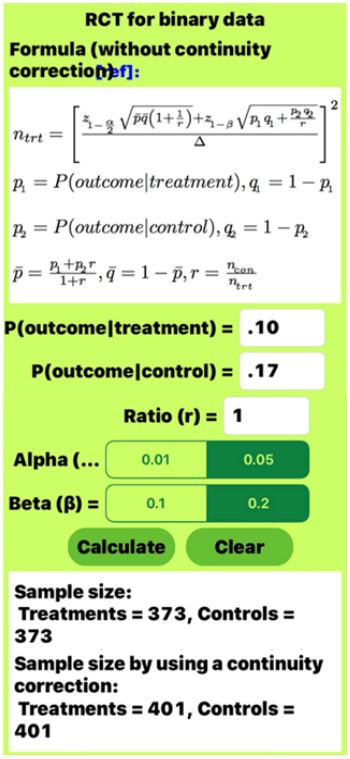
10.8. Study termination criteria

Interim analysis every 6 months, study will stop when

- Reintubation rate in nHFO more than 30% (2 time of 15% in Fig. 4)
- Reintubation rate in nSIPPV more than 60% (2 time of 29% in Fig. 2)
- Reintubation rate between nHFO and nSIPPV difference more than 30%

10.9. Sample size calculation





10.10. Study procedure(s)/stage(s)

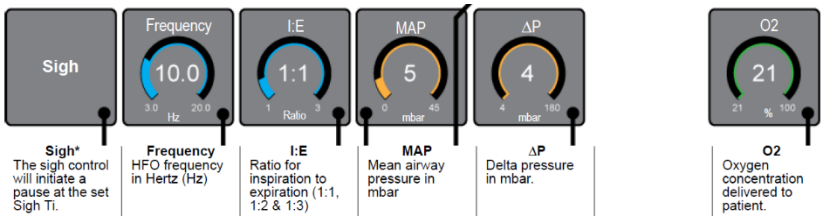
This study was blocked and stratified randomization. Subjects were equally (1:1) randomized to one of the two treatment sequences (nHFOV–nSIPPV, nSIPPV–nHFOV). The allocation sequence was computer generated by box of four. The allocation concealment was ensured by using identical, opaque, sealed envelopes. An envelope was drawn by a dedicated nurse immediately after enrolment of the infant. The participants were stratified by gestational age and oxygen index (OI = mean airway pressure [MAP]*FiO_2*100/PaO_2). The participates were on the non-blinded and randomized NIV mode for 2 hours and blood gas was analyzed then switched to another NIV mode for 2 hours (cross-over) and blood gas was analyzed repeatedly. There was not a washout period between 2 NIV modes then the last NIV mode was on until no need NIV. We will register in ClinicalTrials.gov before start and enrollment of the participants.

Extubation criteria: The ventilated neonate had a targeted oxygen saturation (SpO2 > 90%) during on FiO2 < 0.4 and acceptable blood gas (pH > 7.25, PaCO2 < 60) with the respiratory setting of

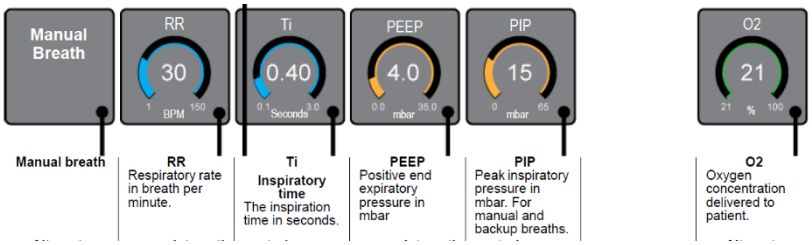
1. HFO: flow 6-10 L/min, frequency 10 Hz, MAP = "6-7 (preterm), 7-9 (term)" cmH_2O, dP = 12-20, I:E = 1:1
2. AC: flow 6-10 L/min, rate 30/minute, PIP 12-15 cmH_2O, PEEP = 3 cmH_2O

Intervention nHFOV and nSIPPV were generated by neonatal ventilators (SLE6000 infant ventilators, United Kingdom) using bi-nasal prongs (RAM cannula, NEOTECH®, USA) or the nasal mask of the same type for both ventilation modes. The size of the prongs was determined by the infant's weight. The largest possible prongs were used, with a snug fit to avoid leakage. Pacifier for preterm and term neonate (Jollypop™, USA) was taken to avoid leakage from the mouth. The disposable ventilator circuit (Fisher & Paykel RT268™, Evaqua Dual Limb Infant Breathing Circuit Kit with Evaqua 2 Technology and Pressure Line, Flow > 4L/min, New Zealand) was used. The initial NIV setting was[7]

1. nHFO: flow 8-10 L/minute, frequency 10 Hz, MAP = “MAP (before extubation) + 2” or “8 (preterm), 10 (term)” cmH_2O, dP = "2-3 times of MAP with visible chest oscillations" or 25-35 cmH_2O, I:E = 1:1, FiO_2 = “FiO_2 (before extubation) + 0.1-0.2” keep targeted SpO_2 90-94%



2. nSIPPV: flow 8-10 L/minute, rate 60/minute, PIP = “PIP (before extubation) + 2-5” or “20 (preterm), 25 (term)” cmH_2O, PEEP = 5 cmH_2O, IT = 0.5 s, FiO_2 = “FiO_2 (before extubation) + 0.1-0.2” keep targeted SpO_2 90-94%. The highest trigger sensitivity avoiding auto triggering was selected.



The monitoring after extubation was vital signs, clinical manifestations, respiratory distress, and umbilical arterial blood gas. The first blood gas before extubation was routine obtained. After randomization, the initial NIV was started then blood gas was obtained after 2 hours. The participant was switched to another NIV and blood gas was obtained after 2 hours. The participant was continued with the last NIV mode until the NIV was stopped. The participant was excluded if severe respiratory failure with reintubation during 4 hours after intervention. The parameters were adjusted or titrated according to patient tolerance and disappeared respiratory distress, the intervention went on until 4 hours. The NIV was stopped to “room air, oxygen box, low or high flow cannula” when

1. nHFO: MAP = 5-6 cmH_2O, dP = 10-15
2. nSIPPV: PIP/PEEP = 10-12/3-5 cmH_2O

Criteria for extubation failure or reintubation were as follows:

1. Cardiorespiratory arrest or any type of pulmonary hemorrhage
2. Persistent low blood pressure without response to volume expander and vasoactive agents
3. Stupor or persistent drowsiness after initial correction and care
4. Severe respiratory distress
5. Two hours of respiratory acidosis with $PaCO_2$ > 70 mmHg and pH < 7.2
6. Two hours of hypoxia with PO_2 < 50 mmHg with FiO_2 > 0.6, and maximal pressures given (MAP 20 and PIP 25 cmH_2O in the nHFOV and nSIPPV group, respectively)
7. Apnea occurring three or more times per hour and a heart rate less than 100/min or apnea with required bag-and-mask ventilation.
8. Severe post extubation stridor

In case of extubation failure, the study period was ended prematurely for the respective infant, pCO_2 was measured by blood gas analysis and a mode of ventilation was chosen as

deemed appropriate by the attending staff. In general, infants were treated with intravenous aminophylline then oral caffeine base and were supported before and after the study.

10.11. Study instrument(s) and outcome measurement(s)

The ventilator modes for nSIPPV and nHFO are SLE 6000 (United Kingdom). Nasal mask for interface. Blood gas and electrolytes analyzer ABL800 BASIC (Radiometer Medical ApS™, Denmark).

10.12. Data collection methodology

Participant's data and blood gas's result will be recorded in record form.

10.13. Data management

EpiData entry is used for data entry and data documentation. The data will be safe and private collected; moreover, only principal investigator and recorder will access.

10.14. Statistical analysis

Descriptive part: Mean (SD), Median ± IQR

Analytic part: Continuous outcome

1. Carry-over effect = Independent t-test comparing intraindividual sums of measurements from both periods.
2. Treatment effect = Independent t-test comparing intraindividual differences of measurements of nHFOV versus nSIPPV from both periods.
3. Dependent t-test

Regression analysis

Category (reintubation): logistic regression

Time to event (reintubation): Cox's proportion model

Intention-to-treat analysis was applied in case of treatment failure.

$p < .05$ was considered significant

Subgroup analysis was performed

11. Ethical consideration

11.1. Possible risks/effects in the study, including preventive and alleviation measures

Both interventions, the participants were obtained the blood samples before and after intervention via arterial line to minimize pain from phlebotomy.

The volume of blood sample was 0.4 mL including before and after tests. The maximum allowable blood draw volumes were shown in **Figure 6.**

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Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20

Figure 6 Maximum allowable blood draw volumes

11.2. Describe the process/system for assuring confidentiality and the privacy of the research participants/communities

The record form was unidentifiable enrolled patients; therefore, name or hospital number would not be filled in the record form. The data would be kept in secret files and only principal investigators and recorders could access to these data during recruitment of the participants, during data collection, during transcription, and data analysis, and dissemination of research results.

11.3. Benefits of the study for participants and the community/country including how findings of the study use for strengthening community.

The result of this study may be the choice of post-extubation via nSIPPV and nHFO (head to head comparison)

11.4. Informed consent process: Process/method of invitation the participants to participate in the research, such as personal contact, referral from other(s), brochure, and announcement, etc.

The parents of intubated neonates without exclusion criteria would be pursued to enrolled in this study by the dedicated nurse. The parents would receive informative documents with explaining the entire data about 30 to 60 minutes or until the parent were crystal clear about the study detail by the nurse. If the parents allowed the patients to enroll in the study, they would sign the signature in the informed consent's document.

11.5. Procedure specifying for research participant withdrawal from the study

If enrolled participant met the withdrawal criteria, the participant was withdrawal and not replaced. The subjects withdrawn were followed-up as routine care.

11.6. Clearly indicate person(s) responsible for payment for treatment of complications and adverse effects

None

11.7. Compensation for research participant

Yes, please provide detail:.....

☒ No, please provide reasons: there was pragmatic trial and routine preterm care.

11.8. Does the study involve biological specimen collection? If yes, also explain how the investigator manages the leftover specimen.

None

11.9. Research project with special ethical consideration *(if applicable)*

This study involved in vulnerable subjects.

12. Limitation(s) and barrier(s) of the study *(If applicable)* and plans for mitigation

This study involved in vulnerable subjects, so the enrolled participants may not reach to targeted numbers of the calculated sample size. We need to closed monitor and progress to the REC every 6 months. If slow rate of enrollment may extend the duration or terminate of the study.

13. Time schedule of the study

Duration of the study: 3 years 10 months

14. Budget detail of the study

Funded by: ..... Budget amount: .....

☒ Expecting funded from: Research Grants, Faculty of Medicine, Prince of Songkla University
Budget amount: 450,000 Baht
Private fund..... Budget amount: .....

15. Expected outcomes of the study

- Paper was published in database ISI at least 1 paper
- For resident training of pediatric certification

16. References

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Researcher certification

The principal investigator (and advisor) listed and signed below, will make certain that

- The study processes will be strictly conducted following the proposal that has been approved by the office of Human Research Ethics Unit and in accordance with all principles of health-related research involving human.
- The study processes will be conducted in accordance with the Standard Operational Procedures (SOP) of the of Human Research Ethics Unit including report of protocol amendment, progression, serious adverse event, deviation, and final summary.

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(Anucha Thatrimontrichai)
Date 15 October 2019
Principal Investigator