

## Heated, humidified high-flow nasal cannula vs. nasal CPAP in infants with moderate respiratory distress

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### Abstract

**Background** Respiratory distress is the most common cause of morbidity in premature babies in the delivery room. Nasal continuous positive airway pressure (nCPAP) is widely used as the preferred modality of treatment, although it may cause nasal trauma. Heated, humidified high-flow nasal (HHHFN) cannula is an alternative oxygen therapy, yet the safety and efficacy has not been widely studied.

**Objective** To compare the safety and efficacy of HHHFN and nCPAP in premature babies with gestational age > 28 to < 35 weeks and moderate respiratory distress.

**Methods** We conducted a randomized, non-inferiority, clinical trial using HHHFN vs. nCPAP as a treatment for moderate respiratory distress within 72 hours after they had been used. The efficacy endpoints were treatment failure, length of device uses, length of Kangaroo Mother Care (KMC), and full enteral feeding time. Safety assessment included pain score, nasal trauma, and systemic complications.

**Results** No differences were found in terms of incidence of endotracheal intubation within < 72 hours of HHHFN (20%) compared to nCPAP (18%) ( $P=0.799$ ). However, there was a significant difference in moderate nasal trauma in nCPAP (14%) compared to HHHFN (0%) ( $P=0.006$ ). There were no significant differences of blood gas analysis results, full enteral feeding time, length of KMC, length of device uses, and rate of complications (bronchopulmonary dysplasia/BPD, intraventricular hemorrhage/IVH, patent ductus arteriosus/PDA, necrotizing enterocolitis/NEC and late onset neonatal sepsis/LONS) between the nCPAP and HHHFN groups.

**Conclusion** The HHHFN is not inferior to nCPAP in terms of the safety and efficacy as primary non-invasive therapy in premature babies of gestational age > 28 to < 35 weeks with moderate respiratory distress. Compared to nCPAP, HHHFN induced lower nasal trauma. [Paediatr Indones. 2019;59:331-9; doi: <http://dx.doi.org/10.14238/pi59.6.2019.331-9>].

**Keywords:** premature; nCPAP; HHHFN; respiratory distress; non-inferiority trial

Respiratory distress in neonates should be handled with care and as early as possible to prevent further complications or even death. Neonatal stabilization consists of preventing hypothermia, airway management, supporting optimal respiration and adequate circulation, as well as preventing hypoglycemia, which should be performed in all cases of respiratory distress, regardless of their etiology.<sup>1</sup> In general, non-invasive or invasive ventilation therapy is given to prevent respiratory failure. Endotracheal intubation is the limit of invasive ventilation therapy.<sup>2</sup>

Based on animal studies, invasive ventilation therapy, even for short durations, was associated with decreased lung function, which induced alveolar inflammation and surfactant deactivation, as well as repression of alveolar growth. Excessive tidal volume (more than 6 ml/kg body weight) leads to ventilator-induced lung injury (VILI). Atelectrauma, which is alveolar trauma associated with less than optimal airway opening, induces the production of biochemical

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mediators that lead to inflammation of lung tissue (biotrauma). Ventilator-induced lung injury is closely related to increased incidence of bronchopulmonary dysplasia.<sup>3</sup>

Currently, nasal continuous positive airway pressure (nCPAP) is the first choice of non-invasive ventilation therapy in infants with respiratory distress. Nasal CPAP is used for both primary therapy, such as in respiratory distress syndrome, obstructive apnea, neonatal pneumonia, and meconium aspiration syndrome, as well as secondary therapy, such as in post-extubation from a mechanical ventilator. Studies have shown the benefits of nCPAP to be alveoli recruitment, preventing alveolar collapse, decreasing lung resistance, maintaining an open airway, as well as increasing lung residual capacity, transpulmonary pressure, and lung compliance. Despite its many advantages, the application of nCPAP is not always easy, with problems varying from nCPAP dislodgement, nasal trauma, and infant discomfort to difficulty applying Kangaroo Mother Care.<sup>4,5</sup>

Many neonatal intensive care units now use heated, humidified high-flow nasal (HHHFN) cannula for respiratory distress in newborns. Despite the limited studies about its safety and efficacy, HHHFN continues to gain popularity among neonatologists. Clinical trials have provided evidence for its effectivity as both primary and secondary therapy, while others have conflicting results. HHHFN is a method to provide respiratory support using a high-speed ( $> 2$  L/min), warmed ( $37^{\circ}\text{C}$ ), and humidified (100% relative humidity or containing  $\text{H}_2\text{O}$  44 mg/L) airflow through a nasal cannula. Some advantages of HHHFN are improved lung compliance and alveolar-capillary gas fraction exchange, as well as reduced upper airway dead space, airway resistance, burden of body metabolism in respiratory air conditioning function, in addition to decreased work of breathing and positive airway pressure creation for lung recruitment.<sup>6-9</sup>

A Cochrane's meta-analysis concluded that more clinical studies with good design are needed in order to provide evidence for the effectivity and efficacy of HHHFN compared to nCPAP, as initial treatment of respiratory distress in infants.<sup>7</sup> Such study should be done, not only in developed countries, but also in developing countries, especially in densely-populated nations with high newborn mortality rates and low antenatal steroid coverage. Therefore, we aimed to

conduct a clinical study to compare the safety and efficacy of HHHFN to nCPAP as a primary therapy modality in preterm infants.

## Methods

This study was a non-inferiority, randomized, clinical trial to determine treatment failure/success within 72 hours of treatment between HHHFN and nCPAP in the management of moderate respiratory distress in preterm newborns. It was undertaken at the national referral neonatal intensive care unit (NICU) at Cipto Mangunkusumo Hospital from June to September 2017.

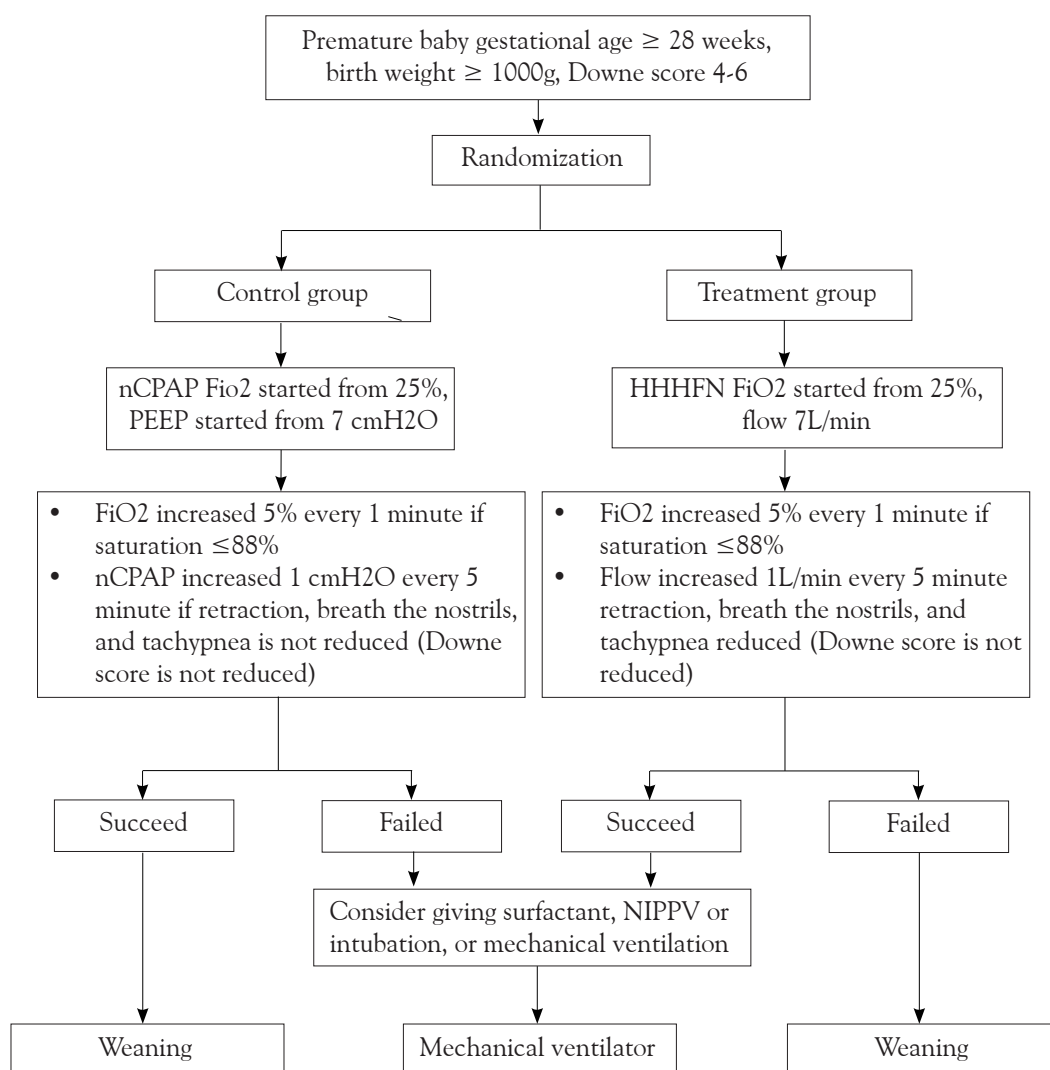
Subjects who met the inclusion criteria were allocated with a computerized, four-block, randomization technique to the treatment group, HHHFN, or the control group, nCPAP. The inclusion criteria were neonates with gestational age  $\geq 28$  to  $< 35$  weeks, birth weight  $\geq 1,000$  grams, moderate respiratory distress (Downe's score  $< 6$ ) from birth or  $< 24$  hours of age, and had never received prior non-invasive ventilation support. The exclusion criteria were severe respiratory distress (Downe's score  $\geq 6$ ), recurrent apnea  $> 2$  times in 1 hour, respiratory distress due to problems outside the lungs, congenital anomalies that aggravated the respiratory distress, contraindication of using non-invasive ventilation (e.g., hernia diafragmatica), congenital metabolism abnormalities, and requiring surfactant therapy. This study was approved by the Research Ethics Committee of the University of Indonesia Medical School and the Research Ethics Committee of Cipto Mangunkusumo Hospital.

Gestational age was determined by the New Ballard score.<sup>10</sup> The degree of respiratory distress was quantified by Downe's score.<sup>11,12</sup> The control group was supported with non-invasive ventilation of nCPAP using a BC 161 Bubble CPAP system (Fisher Paykel®), while the infants in the treatment group received HHHFN using an optiflow premature system (Fisher Paykel®). Blood gas analysis was measured using *pHOx Ultra*® (Nova Biomedical) machine. Peripheral saturation was read by radical 7 pulse oximetry (*Massimo*®). Pain score was quantified using the Cipto Mangunkusumo Hospital neonatal pain monitoring score adopted from the Neonatal Pain

Assessment tool.<sup>13</sup> Nasal trauma due to the nasal prong was assessed by Fisher score.<sup>13</sup> The duration of full enteral feeding time was measured in hours, with rounding up to 1 day if  $\geq 12$  hours. Both HHFN and nCPAP were applied as early as respiratory distress detected, whether in delivery room or in neonatal care unit. Failure was defined when the baby got intubated less than 72 hours of treatment, while success was defined when the baby has never been intubated. The study protocol flow chart is shown in **Figure 1**.

## Results

This study was conducted from June to September 2017. A total of 169 babies were born with gestational age  $\geq 28$  to  $< 35$  weeks in Cipto Mangunkusumo Hospital, 100 of whom met the inclusion criteria. The study flow chart with outcomes is shown in **Figure 2**. The post natal maternal and infant characteristics data were not significantly different between the nCPAP and HHFN groups (**Table 1**).



Note: NIPPV = non-invasive positive pressure ventilation

**Figure 1.** A flow diagram of study recruitment

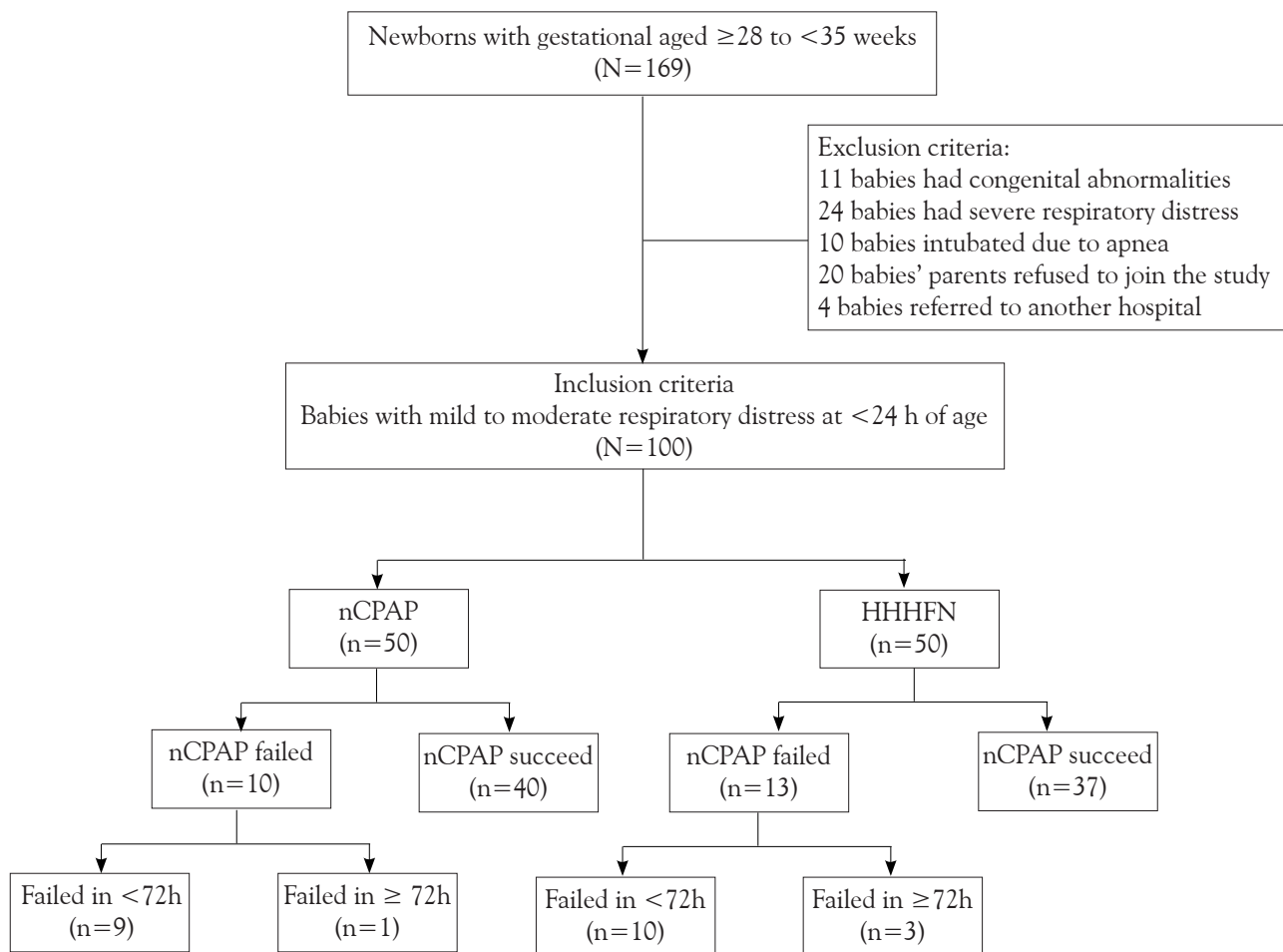
**Table 1.** Characteristics of maternal and infant data

Characteristics		nCPAP (n=50)	HHHFN (n=50)
Maternal	Chorioamnionitis, n (%)		
	Yes	2 (4)	1 (2)
	No	48 (96)	49 (98)
	Antenatal care, n (%)		
	Regular	44 (88)	47 (94)
	Irregular	6 (88)	3 (94)
	Premature rupture of membranes, n (%)		
	< 18 hours	31 (62)	29 (58)
	≥ 18 hours	19 (38)	21 (42)
	Urinary tract infection, n (%)		
	Yes	2 (4)	2 (4)
	No	48 (96)	48 (96)
	Hypertension during pregnancy, n (%)		
	Yes	13 (26)	14 (28)
	No	37 (74)	36 (72)
	Hyperglycemia during pregnancy, n (%)		
	Yes	2 (4)	0 (0)
No	48 (96)	50 (100)	
Antenatal steroids, n (%)			
Incomplete	33 (66)	35 (70)	
Complete	7 (34)	15 (30)	
Antenatal hemorrhage, n (%)			
Yes	2 (4)	6 (12)	
No	48 (96)	46 (88)	
Infant	Gender, n (%)		
	Male	22 (44)	23 (46)
	Female	28 (56)	27 (54)
	Median gestational age (range), weeks	33 (28-34)	33 (28-34)
	Median birth weight (range), grams	1,695 (1,010-2,735)	1,710 (1,002-2,600)
	Type of delivery, n (%)		
	Vaginal	12 (24)	15 (30)
	Caesarian section	38 (76)	35 (70)
	History of resuscitation, n (%)		
	None	12 (24)	14 (28)
	Early nCPAP, HHHFN	31 (62)	28 (56)
	VTP without intubation	5 (10)	8 (16)
	Crystalloid support	2 (4)	0 (0)
	Chest compressions and adrenaline	0 (0)	0 (0)
	Median Downe score (range)	5 (4-6)	5 (4-6)
	Radiology diagnosis, n (%)		
	TTN or RDS grade 1-2	44 (88)	44 (88)
RDS grade 3-4, MAS, pneumonia, others	6 (12)	6 (12)	
Early-onset neonatal sepsis, n (%)	1 (2)	3 (6)	

TTN=transient tachypnea of the newborn, MAS=meconium aspiration syndrome

There was no significant difference related to the treatment failure between HHHFN and nCPAP, blood gas analysis results, length of full enteral feeding

and KMC (Tables 2, 3, 4). Moderate nasal trauma was found more frequent in nCPAP group compared to HHHFN group ( $P=0.006$ ).



**Figure 2.** Study outcomes flow chart

**Table 2.** Comparison of failure rates and nasal trauma between the nCPAP and HHHFN groups

		nCPAP (n=50)	HHHFN (n=50)	P value
Treatment failure	Failed ≤72 hours, n(%)	No	41 (82)	0.799*
		Yes	9 (18)	
	Failed >72 hours, n(%)	No	49 (88)	0.309*
		Yes	1 (2)	
Nasal trauma at 3 days post-treatment	None or grade 1	43 (86)	50 (100)	0.006*
	Grade 2 or 3	7 (14)	0	

**Table 3.** Comparison of pH, pCO<sub>2</sub>, and arterial blood pO<sub>2</sub> levels between nCPAP and HHHFN groups

	Mean nCPAP (SD)	Mean HHHFN (SD)	Mean difference (95%CI)	P value
pH	7.42 (0.10)	7.40 (0.09)	0.02 (-0.16 to 0.59)	0.259*
pCO <sub>2</sub> , mmHg	37.65 (12.98)	41.37 (11.82)	-3.72 (-8.65 to 1.20)	0.137*
pO <sub>2</sub> , mmHg	66.98 (30.69)	72.80 (37.46)	-5.81 (-19.41 to 7.78)	0.398*

**Table 4.** Comparison of length of device usage, mean pain score, length of full enteral feeding time, and length of KMC between the nCPAP and HHHFN groups

	Median nCPAP (range)	Median HHHFN (range)	P value
Length of device usage, hours	25 (1-425)	27 (1-644)	0.537*
Mean pain score	2.33 (1.33-5.66)	2.33 (1.33-6.00)	0.502*
Time to full enteral feeding, days	6 (1-24)	7 (1-28)	0.959*
Length of KMC, hours	0 (0-25)	0 (0-28)	0.724*

## Discussion

To our knowledge, this is the first study to compare the safety and efficacy of HHHFN and nCPAP as primary therapy while still in the delivery room. It is our standard to give nCPAP to babies who experience respiratory distress using cold and dry air via t-piece rescucitaor and single nasal prong. In our study we tried to give HHHFN as early as possible while still in the delivery room based on the idea that HHHFN could also provide positive airway pressure compared to nCPAP if given with an appropriate gas flow.<sup>13,14</sup>

Contrary to other studies that started HHHFN at different flow rates (Yoder *et al.* 3-5 L/min,<sup>8</sup> Iranpour *et al.* 1.5-3L/min,<sup>14</sup> Roberts *et al.* 6-8 L/min,<sup>15</sup> Shin *et al.* 3-7 L/min,<sup>16</sup> Ciufini *et al.* 4-6 L/min,<sup>17</sup>), we started HHHFN at 7 L/min. We expected that creating greater positive airway pressure would be more helpful for the neonates to pass the transition period from the time they were in the delivery room.<sup>13,14</sup>

Our subjects had a greater failure proportion in both the nCPAP and HHHFN groups compared to studies done in developed countries (USA, Australia and Norway).<sup>15,17,18</sup> There were 68 babies whose mothers did not complete steroid antenatal course, and 32 babies completed steroid antenatal course. Failure happened in 25% and 18% babies whose mother had not completed and completed antenatal steroid course, accordingly. This higher failure rate may have been due to incomplete or lack of antenatal steroid administration that 92.3% of subjects experienced respiratory distress caused by transient tachypnea of the newborn or grade 1 respiratory distress syndrome, both of which tend to improve rapidly. There were 74 babies who got HHHFN or nCPAP early in the delivery room, while 26 babies got late respiratory distress and started to get HHHFN or nCPAP in neonatal care unit. There was 25% failure rate for babies who got respiratory support early in the

delivery room, and 15% failure rate for babies who got late respiratory support in neonatal care unit.

Our results were in agreement with other studies in that preterm babies had shorter treatment duration with nCPAP than with HHHFN, yet the difference was not statistically significant.<sup>8,15,16</sup> This result might have been due to nCPAP having more stable (non-fluctuative) positive pressure airflow compared to HHHFN.<sup>13,14,18</sup> In fact, from its conception, HHHFN was not intended to deliver positive pressure, but high continuous airflow, which eventually creates airway pressure whenever there is airway resistance.<sup>18</sup>

The benefit of using HHHFN is that the continuous airflow can reduce the respiratory loss space, such that ventilation becomes more effective. Upon infant inspiration, if the inspiratory airflow is lower than HHHFN airflow, additional airflow will enter the airway. On the contrary, during expiration, the difference in directions of expiratory airflow to the HHHFN continuous flow creates airway pressure opening.<sup>4,9,18</sup>

There were no significant differences between pH, pCO<sub>2</sub>, and pO<sub>2</sub> at 30 to 60 minutes post-nCPAP usage compared to HHHFN. This finding indicates that airway pressure and ventilation were comparable between the nCPAP and HHHFN groups. Because partial pressure of arterial blood oxygen is strongly influenced by partial pressure of alveolar oxygen,<sup>2,19,20,23,24</sup> degree of alveolar expansion is strongly influenced by positive airway pressure, and there were no significant differences in FiO<sub>2</sub> usage between the two groups on blood gas analysis, we can conclude that the positive airway pressure is comparable in both devices.

The partial pressure of carbon dioxide in blood is determined by degree of CO<sub>2</sub> exhaustion, known as minute ventilation. Tidal volume and respiratory rate are the two determining factors of minute ventilation. If the respiratory rate is assumed to be comparable

between groups (comparable tachypnea determinant factors such as Downes score, birth weight, gestational age, and pain score), then the tidal volumes in both research groups were comparable. With regards to similar birth weight, gestational age, and thorax x-ray, we can conclude that positive airway pressure created comparable tidal volumes in both groups.

There were no significant differences in median duration of nCPAP and HHHFN usage [25 (range 0-425) hours and 27 (range 0-644) hours, respectively]. These durations were shorter than the median (interquartile) reported by Manley *et al.* for nCPAP [48 (48-168) hours] and for HHHFN [72 (48-144) hours].<sup>18</sup> These differences were probably caused by the older gestational age (median 33 weeks) of our subjects compared to theirs (median 32 weeks).<sup>18</sup> Another possibility was our limiting subject inclusion to only preterm babies with moderate respiratory distress. As such, 60% of the etiology of subjects' respiratory distress was TTN or 1st to 2nd degree hyaline membrane disease (HMD), which naturally get better faster.<sup>16,18</sup>

We measured pain score in the first three days on the premise that most non-invasive airway support will be stopped in less than 72 hours. We suspected that the degree of pain was correlated to nCPAP and HHHFN application. There were no differences in median pain score between the nCPAP or HHHFN groups. These findings might have been due to nursing skill improvements in conducting a neonatal comfort program, such as pain score measuring as a vital sign, early intervention if subject experience painful stimuli, newborn nest usage, midline position in babies, hydroxycollid tape to prevent blisters, minimal handling program, and giving sucrose and/or pacifier for non-nutritive sucking.<sup>21,22</sup> Similarly, Klingenberg *et al.* compared pain scores in babies given nCPAP and HHHFN and found that mean cumulative Edin scores were 10.7 and 11.1, respectively; ( $P=0.25$ ).<sup>23</sup>

In our study, we measured the time to full enteral feeding, not full oral feeding, for study feasibility, and found no significant difference between the two groups [6 (range 1-24) vs. 7 (1-28) days; ( $P=0.959$ )]. Shin *et al.* in Korea also reported median (interquartile) achievement of full enteral feeding in babies > 30 weeks with nCPAP or HHHFN were 6 (5-9.5) days and 6 (5-9) days, respectively.<sup>16</sup> This observation was likely due to the application of

an aggressive enteral nutrition program soon after infants are stable in our unit.<sup>24</sup> With dyspnea quickly resolved (nCPAP and HHHFN median usage of 25 and 27 hours, respectively), the sooner the infant's condition stabilizes, hence, the sooner the infant achieves enteral feeding.<sup>24,25</sup> This program manages to overcome factors that delay reaching full enteral feeding, such as hesitation due to aspiration risk in increasing feeding volume as long as the babies are still in positive airway pressure support, increased abdominal circumference, and vomiting.<sup>26</sup>

Subjects' median weight was 1,800 grams and median gestational age was 33 weeks. Such infants will benefit from Kangaroo Mother Care (KMC). However, 80% of our subjects' mothers did not do KMC. Low KMC duration in babies undergoing nCPAP or HHHFN may be caused by mother's lack of awareness of the importance of intermittent KMC, limited supporting facilities such as KMC chair, inexpensive and comfortable accommodation for mothers in the hospital area, and poor road conditions that make it difficult for the mother to make frequent trips to the hospital. Unfortunately, we did not measure the duration of desaturation episodes during KMC. Nor did we analyze KMC duration post-nCPAP or post-HHHFN, due to the limited observation period and the fact that it was a peripheral issue to our study aim.

Although our hospital used hydroxycollid tape (*Duoderm Extra-Thin*®) around subjects' noses to prevent nasal trauma during nCPAP, 7 babies (14%) from the nCPAP group experienced 2nd degree nasal trauma. In contrast, no babies had nasal trauma in the HHHFN group. Similarly, a study compared nasal trauma degree between nCPAP and HHHFN usage and reported significantly higher mean (SD) nasal trauma degree with nCPAP [11.7 (10.4)] than with HHHFN [2.8 (5.7)]; ( $P < 0.001$ ).<sup>27</sup> All 7 infants with 2nd degree nasal trauma were < 32 weeks gestational age, had birth weight between 1,020 to 1,210 grams, and were in the nCPAP group. Based on our observation, the large size of the nasal prong and inability to switch to HHHFN (due to study protocol) were the main causes of the 2<sup>nd</sup> degree nasal trauma problem.

Warm and humid air helps maintain optimal infant skin integrity. Chang *et al.* noted in an *in vitro* study that there were significant mean (SD)

differences in warm air in HHHFN [83 (3.1)%] compared to nCPAP [76 (0.81)%], with 3-8 L/minute air flow. This might have been another factor in preventing nasal trauma.

Fifteen percent was considered to be the significant difference in this non-inferiority study. Ideally, the largest percentage difference for a non-inferiority study is < 10%. However, if we apply this principle to our study, we would have needed 350-400 subjects. Another multicenter, non-inferiority clinical study is needed to acquire more subjects. However, there was congruence from the 9 outcomes in our study, indicating that efficacy and safety OF HHHFN and nCPAP therapy were not that different in infants of gestational age > 28 to < 35 weeks with moderate respiratory distress.

Intra-tracheal pressure measurement is the gold standard in comparing positive airway pressure between nCPAP and HHHFN. Unfortunately we could not conduct this test due to limited equipment, facility, and cost. However, this study is the first to compare HHHFN and nCPAP as primary therapy from the delivery room with outcomes (pH, pCO<sub>2</sub>, pO<sub>2</sub>, duration of ventilation support, and time until full enteral feeding) that may serve as surrogates for intra-tracheal pressure measurements.

In conclusion, in newborns with gestational age ≥ 28 to < 35 weeks and birth weight ≥ 1,000 grams with moderate respiratory distress syndrome aged less than 24 hours, there are no significant differences in failure of therapy at 72 hours post-device usage, pCO<sub>2</sub>, pO<sub>2</sub>, mean blood pH level in 30 minutes to 1 hour post-device usage, duration of device usage, time until full enteral feeding, or in duration of KMC between those who received nCPAP compared to HHHFN. But, there is a significant difference related to nasal trauma of 2<sup>nd</sup> or 3<sup>rd</sup> degree post-72 hours of usage between the 2 groups.

From these findings, we suggest that heated, humidified high-flow nasal cannula can be an alternative, non-invasive positive airway therapy in infants ≥ 28 to < 35 weeks gestational age with moderate respiratory distress, and aged less than 24 hours. Similar multicenter studies are needed with a larger sample size and infants with gestational age ≤ 28 weeks. Both HHHFN and nCPAP are better if warmed (36.5-37.5°C) and humid (containing water vapor 44 mg/L) gas sources are used.

## Conflict of interest

None declared.

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