The Effectiveness of the Heated Humidified High Flow Nasal Cannula as a Noninvasive Respiratory Support for Preterm Infants for Prevention of Extubation Failure

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Authors' contributions

This work was carried out in collaboration among all authors. Author SMN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MRES and HSEM managed the analyses of the study. Author MMA managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aims: To compare the efficacy and safety of the HHHFNC as a post extubation respiratory support of preterm infants who were initially required endotracheal intubation and conventional mechanical ventilator after birth at different flow rates (3 L/min and 6 L/min).
Study Design: A Randomized controlled trial.
Place and Duration of Study: Neonatal Intensive Care Unit, Pediatrics department, Tanta University Hospitals, over one-year period, from December 2018 to December 2019.
Methodology: 30 preterm, with gestational age (30-36) weeks and birth weight ≥ 1300 g, were randomized to receive HHHFNC at either flow rate 3 or 6 L\min to prevent postextubation failure. Primary outcomes: the incidence of treatment failure of the HHHFNC at flow 3 and 6 L/min, which will require n CPAP or NIMV, or will require reintubation after successful extubation within 72 h.

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Secondary outcomes: rate of deaths within 72 hours post extubation, the total duration of all types of oxygen support, total duration of hospitalization and incidence of neonatal morbidities such as nasal trauma, BPD, symptomatic PDA, IVH ≥ grade II, pneumothorax, pulmonary hemorrhage, ROP, apnea, sepsis and NEC ≥ stage II.

Results: The incidence of need for higher flow rate of HHHFNC (n =17, 56.6%) , the need for n CPAP or NIMV after failure of higher flow rate of HHHFNC (n =16, 53.3%), the need for intubation & MV (n =7, 23.3%), the incidence of nasal trauma (n =9, 30%), BPD (n =9, 30%) , IVH ≥ II (n =7, 23.3%) , NEC ≥ II (n =0), pneumothorax (n =5, 16.6%) , pulmonary haemorrhage (n =3, 10%), death (n =3, 10%), median duration of hospitalization in days =22.5 (17-28), median duration of all oxygen support in days = 18 (15-21), so the failure rate was 17 out of 30 (56.6%).

Conclusion: HHHFNC use is noninferior to other forms of noninvasive respiratory support in preterm infants for prevention of extubation failure. There were better outcomes of HHHFNC with higher gestational age and birth weight in preterm infants at either flow rates 3 or 6 L/min.

Keywords: Heated humidified high flow nasal cannula (HHHFNC); noninvasive; postextubation; preterm; respiratory distress.

ABBREVIATION

BPD   : *Bronchopulmonary Dysplasia*
PDA   : *Patent Ductus Arteriosus*
IVH   : *Intraventricular Hemorrhage*
ROP   : *Retinopathy Of Prematurity*
NEC   : *Necrotizing Enterocolitis*
n CPAP : *Nasal Continuous Positive Airway Pressure*
NIMV   : *Noninvasive Mechanical Ventilation*

1. INTRODUCTION

Preterm babies are born alive before 37 weeks of pregnancy are completed [1]. 15 million babies are born too soon every year [2]:

More than 1 in 10 babies are born preterm, affecting families all around the world [2].

Over 1 million children die each year due to complications of preterm birth. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems [2].

Premature births are responsible for 70% of neonatal mortality, 36% of infant mortality and 25-50% of long-term neurological disabilities. In the last 20 years with the scientific and technological developments observed in the field of neonatology, the survival rate of premature infants has significantly increased [3].

In the high-income countries, almost 95% of those born at 28 to 32 weeks survive, with more than 90% surviving without impairment. In contrast, in many low-income countries, only 30% of those born at 28 to 32 weeks survive, with almost all those born at <28 weeks dying in the first few days of life [4].

Preterm neonates can develop many complications such as respiratory distress syndrome (RDS), IVH, NEC, BPD, neonatal sepsis, PDA, ROP and hyperbilirubinemia [5].

RDS is considered the major reason for increased mortality and morbidity among infants. It occurs in infants whose lungs have not yet fully developed. The more premature the baby is, the higher the chance of RDS after birth [6].

In the past, endotracheal intubation was the main respiratory support in preterm infants, but prolonged intubation can increase risks of infection, lung injury, and chronic lung disease. Therefore, the strategy has been shifted to initiate non-invasive respiratory support as soon as possible to minimize duration of mechanical ventilator [7].

Respiratory support is being achieved more frequently with n CPAP and other less invasive approaches, such as the technique of intubation, surfactant, and extubation (INSURE) [8].

The HHHFNC is not only used as a primary respiratory support but also used after extubation to prevent alveolar collapse. However, it also has some drawbacks such as nasal trauma, head deformity, gaseous bowel distension and the difficulty to maintain the device on infant's face at all time to obtain the constant pressure [9].

The recent randomized controlled studies illustrated the safety and efficacy of HHHFNC for prevention of extubation failure [10,11]. Even

though these trials used different extubation protocols, all concluded that it is as effective as or non-inferior to n CPAP. Nonetheless, the latest systematic review states that the safety and efficacy of HHHFNC still needs further study, especially in extremely preterm subgroup [12].

It has been used as a respiratory support for various purposes including apnea of prematurity [13], primary respiratory support in RDS [14], CPAP weaning [15] and postextubation [16].

Also, it is increasingly being applied in other clinical areas including during neonatal transport and for initial delivery room stabilization of premature infants [17,18,19].

2. MATERIALS AND METHODS

Study place: Neonatal Intensive Care Unit (NICU), Pediatrics Department, Tanta University Hospitals.

Study duration: one year (from December 2018 to December 2019.

Study type: Randomized controlled trial, written informed permissions obtained from all parents or guardians of the neonates.

Data collection: this study included total forty-five preterm neonates after being successfully extubated.

In this study, we enrolled total 45 preterm neonates after being successfully extubated (15 preterm infants were excluded due to major congenital malformations, or congenital heart disease).

This study was a randomized controlled trial. Simple randomization was performed by using computed generated random numbers. It was double blinded with fixed and standard protocols for initiation, weaning, extubation and identification of treatment failure.

➢ 30 included preterm neonates, with gestational age ≥ 30 weeks and less than 37 weeks, who required intubation on admission and extubated from the conventional mechanical ventilator and randomized to receive the HHHFNC (Fisher & Paykel Optiflow System, Healthcare, Auckland, New Zealand) [20].

➢ The main group was subclassified into subgroup A started at flow rate 3 L\min. and subgroup B started at flow rate 6 L\min.

2.1 Criteria of Extubation

• Preterm neonates were considered to be ready for extubation when the settings of ventilator were at peak inspiratory pressure (PIP) of ≤ 15cm H_2O, positive end-expiratory pressure (PEEP) of ≤ 6 cm H_2O, fraction of inspired oxygen (FiO_2) of ≤ 0.3 and intermittent mandatory rate of ≤ 20/min, and have an acceptable blood gas (pH ≥ 7.25, $PaCO_2$ ≤ 55) and hematocrit of > 30% [7].

2.2 Inclusion Criteria

• Preterm neonates, born of gestational age ≥ 30 weeks and of birth weight ≥ 1300 g, suffering from signs and symptoms of respiratory distress after delivery.

2.3 Exclusion Criteria

• Preterm neonates of gestational age < 30 weeks and of birth weight < 1300 g.
• Preterm neonates with major congenital heart diseases, upper airway anomalies, lung hypoplasia and neuromuscular disorders.
• Full term neonates.

2.4 Usage of the HHHFNC

➢ All infants, ≤ 34 weeks were received IV caffeine citrate either a loading dose of 20 mg/kg/dose or a maintenance dose of 5 mg/kg/day in the first 24 hours.
➢ Infants were treated with HHHFNC (Fisher & Paykel Optiflow System, Healthcare, Auckland, New Zealand) [20], with the orifice diameter of the nasal cannula (2.4 to 2.7 mm) and were fitted to maintain a leak at the nose as recommended by the user manual with the aim of occluding approximately half of the nares.
➢ Flow rates of HHHFNC were modified from 3 into 6 L/min or from 6 into 8 L\min. when needed.
➢ Oxygen saturation targets were maintained at 90-95% on HHHFNC, all infants stayed on this assigned mode of respiratory support until they were able to be managed without any respiratory support.
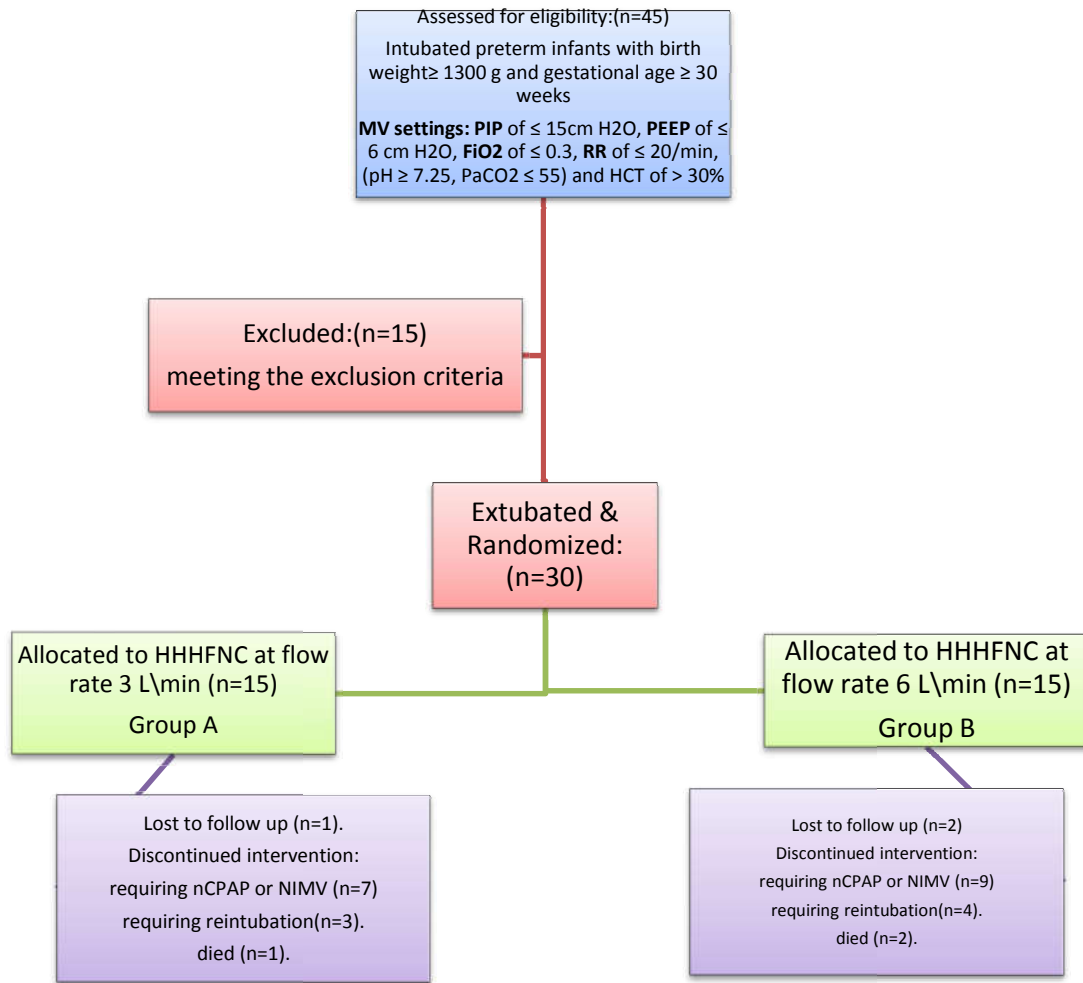
Fig. 1. Participants consort flow diagram
MV: mechanical ventilator, PIP: peak inspiratory pressure, FIO2: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, RR: respiratory rate, HCT: hematocrit

2.5 Weaning from HHHFNC

Treatment with HHHFNC was stopped, as ordered by the treating team, when the infants showed no signs of respiratory distress with room air , weaned to flow rate 2 L\min. and SpO2 > 90%, PCO2 <50 mmHg with FiO2 of 0.21 [21].

2.5.1 HHHFNC treatment failure was indicated by one or more of the following

I.   Respiratory acidosis (PaCO2 > 60 mmHg with pH < 7.25 at maximum setting of the allocated device [flow rate 7-8 L/min]), hypoxia (FiO2 > 0.4 to maintain SpO2 88 to 94%) [21].

II. Significant apnea (> 2–3 episodes of apnea/hour requiring bag and-mask ventilation in 24 hour period or 6 or more apneic episodes requiring tactile stimulation within 6 hours) despite adequate prong fixation and flow [21].

III. Persistent marked/severe retractions.

IV. Urgent need for ETT & MV as in cardiovascular collapse or shock as determined by the treating team.

➢   When a neonate met one or more of the above criteria, increasing flow rate from 3 into 6 L\min. or from 6 into 8 L\min. was done, then application of other type of non-invasive respiratory support device (from HHFNC to n CPAP and from n CPAP to

NIMV) was considered within 6 hours approximately or required MV if indicated.

2.5.2 The HHHFNC outcomes

2.5.2.1 Primary outcomes

The incidence of treatment failure of the HHHFNC at flow 3 L/min and 6 L/min, which will require n CPAP or NIMV, or will require reintubation after successful extubation within 72 hours.

2.5.2.2 Secondary outcomes

1. Rate of deaths within 72 hours post extubation.
2. The total duration of all types of oxygen support.
3. The total duration of hospitalization.
4. Incidence of neonatal morbidities such as nasal trauma, BPD, symptomatic patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH ≥ grade II), pneumothorax, pulmonary hemorrhage, retinopathy of prematurity (ROP), apnea,

sepsis, and necrotizing enterocolitis (NEC ≥ stage II).

2.5.3 All preterm neonates were subjected to the followings

A- Complete history taking which included:

- Peri-natal history.
- Natal history of labor and delivery.
- Resuscitation history.

B- Full clinical examination.
C- Routine laboratory investigations.
D- Chest X-ray.
E- Transcranial US.

2.6 Statistics

Data were analyzed using SPSS 22. Chi-square and t test were used for quantitative and qualitative variables, P < 0.05 was considered as significant level.

3. RESULTS

Our study showed the following results as in the following tables (1-8).

Table 1. Demographic data of subgroup A & B (n=30) showing

	Group A (n = 15)		Group B (n = 15)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	11	73.3	9	60.0	χ^2= 0.600	0.700
Female	4	26.7	6	40.0		
Gestational age (weeks)						
Min. – Max.	30.0 – 35.0		30.0 – 35.0		t= 0.692	0.495
Mean ± SD.	32.07 ± 1.58		31.67 ± 1.59			
Median (IQR)	32.0 (31.0 – 33.0)		32.0 (30.0 – 32.50)			
Mode of delivery						
NVD	4	26.7	3	20.0	χ^2= 0.186	FEp= 1.000
C.S	11	73.3	12	80.0		
Age of start of HHHFNC (days)						
Min. – Max.	3.0 – 12.0		4.0 – 15.0		U= 42.0*	0.003*
Mean ± SD.	6.20 ± 2.27		9.73 ± 3.75			
Median (IQR)	6.0 (5.0 – 7.0)		8.0 (7.0 – 13.0)			

- *There was no significant difference between the two studied subgroups A & B as regard sex, gestational age & mode of delivery.*
- *There was a statistically significant increase as regard age of start of HHHFNC in group B as compared to group A.*

*χ^2: Chi square test; FE: Fisher Exact; U: Mann Whitney test; t: Student t-test; p: p value for comparing between the studied groups.; *: Statistically significant at p ≤ 0.05.; Group A: extubated to HHHFNC at flow rate 3 L\min.; Group B: extubated to HHHFNC at flow rate 6 L\min.; NVD: normal vaginal delivery.; C.S: cesarean section.*

Table 2. Anthropometric measurements of subgroup A & B (n=30) showing

	Group A (n = 15)	Group B (n = 15)	t	P
Weight (kgs)				
Min. – Max.	1.40 – 2.40	1.30 – 2.40	0.803	0.429
Mean ± SD.	1.77 ± 0.23	1.69 ± 0.35		
Median (IQR)	1.80 (1.65 – 1.85)	1.70 (1.40 – 1.80)		
Length (cms)				
Min. – Max.	40.0 – 44.0	40.0 – 45.0	0.425	0.674
Mean ± SD.	41.60 ± 1.58	41.37 ± 1.42		
Median (IQR)	41.0 (40.25 – 43.0)	41.0 (40.25 – 42.0)		
H.C. (cms)				
Min. – Max.	29.0 – 33.0	29.0 – 33.0	0.268	0.790
Mean ± SD.	30.77 ± 1.0	30.87 ± 1.04		
Median (IQR)	30.50 (30.0 – 31.0)	31.0 (30.0 – 31.50)		
Ponderal index				
Min. – Max.	2.0 – 3.0	1.60 – 3.20	0.853	0.401
Mean ± SD.	2.43 ± 0.28	2.33 ± 0.39		
Median (IQR)	2.40 (2.25 – 2.60)	2.40 (2.10 – 2.55)		

- *There was no significant difference between the two studied subgroups A & B as regard weight, length, head circumference and ponderal index.*

χ^2*: Chi square test   FE: Fisher Exact*
U: Mann Whitney test   t: Student t-test
p: p value for comparing between the studied groups.
*: Statistically significant at p ≤ 0.05.
Group A: extubated to HHHFNC at flow rate 3 L\min.
Group B: extubated to HHHFNC at flow rate 6 L\min.
H.C: Head circumference, Ponderal Index = 100 x Weight (grams) / Height^3 (cm).

Table 3. Antenatal risk factors in subgroup A & B (n=30) showing

Antenatal risk factors	Group A (n = 15)		Group B (n = 15)		X^2	P
	No.	%	No.	%		
PROM	8	53.3	11	73.3	1.292	0.256
Pre-eclampsia, eclampsia	5	33.3	1	6.7	3.333	^{FE}P=0.169
Multiple pregnancies	3	20.0	6	40.0	1.429	^{FE}P=0.427
Abruptio placenta, placenta accrete	0	0.0	1	6.7	1.034	^{FE}P=1.000
Negative	0	0.0	0	0.0	–	–
Others: UTI, chorioamnionitis & IDM	2	13.3	3	20.0	0.240	^{FE}P=1.000

- *There was no significant difference between the 2 subgroups A & B as regard all antenatal risk factors including: PROM, Pre-eclampsia, eclampsia, Multiple pregnancies, Abruptio placenta, placenta accrete, Negative and Others: UTI, chorioamnionitis & IDM.*

χ^2*: Chi square test   FE: Fisher Exact*
U: Mann Whitney test   t: Student t-test
p: p value for comparing between the studied groups.
*: Statistically significant at p ≤ 0.05.
Group A: extubated to HHHFNC at flow rate 3 L\min.
Group B: extubated to HHHFNC at flow rate 6 L\min.
PROM: Premature rupture of membranes.
UTI: Urinary tract infections.
IDM: Infant of diabetic mother.

4. DISCUSSSION

In this present study, in the main studied group (HHHFNC used as a post extubation method), as regard the demographic data, anthropometric measurements, antenatal risk factors and causes of extubation failure, there was no significant difference between both low and high

flow rates subgroups A & B. We included 30 preterm infants with mean GA 32 weeks (30-32.5) & mean BW 1700 g (1500 – 1800).

Resulted in the followings : the incidence of need for higher flow rate of HHHFNC (n =17, 56.6%) , the need for n CPAP or NIMV after failure of higher flow rate of HHHFNC (n =16, 53.3%), the need for intubation & MV (n =7, 23.3%), the incidence of nasal trauma (n =9, 30%), BPD (n =9, 30%) , IVH ≥II (n =7, 23.3%) , NEC ≥II (n =0), pneumothorax (n =5, 16.6%) , pulmonary haemorrhage (n =3, 10%), death (n =3, 10%), median duration of hospitalization in days =22.5 (17-28), median duration of all oxygen support in days = 18 (15-21), so the failure rate was 17 out of 30 (56.6%).

This comes in comparison with Soonsawad, et al. [7], who enrolled 24 preterm infants, were randomly applied to the HFNC. They followed the same extubation criteria, the same reintubation indications and used the same Optiflow system with similar defined outcomes. The HFNC group was subdivided into flow rate 6 L\min. if BW ≥ 1000 g and flow rate 4 L\min. if BW < 1000 g, with smaller mean GA 27.5 (26-30) weeks and lower BW 990 (880-1333) g, showed less extubation failure rate (n=8, 33.3%) (6 on CPAP, 2 on MV), this result may be due to the difference in the rescue protocols and the clinical decisions, higher incidence of BPD (40%), higher incidence of NEC ≥II (8.3%), IVH ≥III (8%), higher incidence of nasal trauma (16.7%), no deaths or pneumothorax.

While Razak, et al. [22], who enrolled 32 preterm infants to study the effect of the HHFNC as a post extubation respiratory support and compared to another CPAP group. They used the same Optiflow system at flow rates 5-6 L\min, followed the same failure treatment criteria but different weaning criteria from HHFNC. The included preterm neonates were with mean GA (31±0.8) weeks and mean BW (1360±140) g. they found lower need for reintubation (n=3, 9%), no deaths, lower incidence of BPD (n=4, 12%), nasal trauma (n=0), IVH ≥ III (n =1, 3%), higher incidence of NEC ≥ II (n =2, 6%), air leak (n=0) and shorter duration of hospitalization (23±10 days). They differed from our study due to the retrospective nature of their study, the different followed protocols, flow rates and clinical decisions.

Also in comparison with Taha, et al., [23], who enrolled 333 preterm infants, received HFNC as post extubation, with mean GA (26.5±1.9 weeks) and BW (776± 149 g), showed higher failure rate including higher need for MV (n=177, 53.1%), higher incidence of BPD (n=174, 52.5%), IVH ≥III (n=31, 9.3%), higher incidence of NEC ≥II (n=30, 9%) and longer mean duration of hospitalization =89 days (69-111), this may be explained by the extremely low BW and GA compared to our study. These differences might be due to the different retrospective aspect of their study, longer period (2008-2013) of the study, larger numbers, smaller GA, extremely low BW, different used devices, protocols and clinical decisions.

Mostafa-Gharehbaghi and Mojabi, [24] who enrolled 42 preterm infants, with larger mean BW (1905±464 g) and GA (32.24±1.7 weeks), were treated by the INSURE method and compared to another CPAP group. They were randomly applied to the HFNC via the Optiflow system. They found lower reintubation rate (n=5, 11.9%), less need for CPAP (n=1, 2.38%), higher incidence of Nasal mucosa injury (n=14, 33.33%) and lower incidence of IVH ≥III (n=3, 7.14%). The differences might be due to the different flow rates, rescue and weaning protocols.

Lastly, Akbarian-rad, et al. [25], who enrolled 30 preterm infants, with mean GA (30.45±2 weeks) and BW (1416±493.26 g), were treated by the INSURE method. They were randomly assigned immediately after extubation to HHHFNC. They followed the same extubation criteria. Their results showed lower reintubation rate (n=5, 16.7%), lower incidence of lower incidence of IVH≥III (n=3, 10%), lower incidence of pneumothorax (n=2, 6.66%) and longer duration of hospitalization (34.6±25.2 days), compared to our study. These differences might be due to different used devices, flow rates, defined outcomes and the followed NICUs' protocols.

There was a significant positive relation between gestational age and success rate of HHHFNC as post extubation at flow rate 3 l\min. as showed in subgroup A with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC and not needed for re intubation.

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Table 4. Follow up data of the 2 Subgroups A & B (n=30) showing

	Group A (n = 15)		Group B (n = 15)		Test of Sig.	p
	No.	%	No.	%		
Need for higher flow rate of HHHFNC (3 into 6 l\min. & 6 into 8 l\min.)						
Not needed	4	26.7	9	60.0	χ^2= 3.394	0.065
Needed	11	73.3	6	40.0		
Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
Not needed	8	53.3	6	40.0	χ^2= 0.536	0.464
Needed	7	46.7	9	60.0		
Need for intubation						
Not needed	12	80.0	11	73.3	χ^2= 0.186	[FE]p=
Needed	3	20.0	4	26.7		1.000
Nasal trauma						
None	11	73.3	10	66.7	χ^2= 0.159	[FE]p=
Nasal trauma	4	26.7	5	33.3		1.000
Antibiotics duration (days)						
Min. – Max.	12.0 – 28.0		15.0 – 35.0		U= 55.0[*]	0.016[*]
Mean ± SD.	19.20 ± 5.20		25.47 ± 7.42			
Median (IQR)	17.0 (15.0 – 23.0)		28.0 (19.50 – 30.0)			
Duration of hospitalization (days)						
Min. – Max.	12.0 – 28.0		15.0 – 35.0		U= 55.0[*]	0.016[*]
Mean ± SD.	19.20 ± 5.20		25.47 ± 7.42			
Median (IQR)	17.0(15.0 – 23.0)		28.0(19.50 – 30.0)			
Total duration of all O_2 support (days)						
Min. – Max.	10.0 – 28.0		12.0 – 35.0		t= 2.447[*]	0.022[*]
Mean ± SD.	15.73 ± 4.62		21.13 ± 7.19			
Median (IQR)	15.0 (12.5 – 17.0)		21.0 (15.0 – 26.0)			

- *There was a statistically significant increase as regard duration of antibiotics, hospitalization & all oxygen support in subgroup B as compared to subgroup A.*
- *There was no significant difference between the 2 subgroups A & B as regard follow up data and outcomes of HHHFNC including: need for higher flow rate of HHHFNC (flow rate 3 into 6 & 6 into 8 L\min), need for n CPAP or NIMV after failure of the higher flow rate of HHHFNC, need for intubation and incidence of nasal trauma.*

χ^2: Chi square test ; FE: Fisher Exact; U: Mann Whitney test;
t: Student t-test; p: p value for comparing between the studied groups.;
*: Statistically significant at p ≤ 0.05. Group A: extubated to HHHFNC at flow rate 3 L\min.
Group B: extubated to HHHFNC at flow rate 6 L\min.

This comes in comparison to, Collins, et al. [26], who randomly assigned 67 preterm ventilated infants to Vapotherm HHFNC after extubation. They found lower extubation failure rate in (n=15, 22%). Overall extubation failure rates were greater in infants born at < 28 completed weeks of gestation (n=26, 44%), when compared with 28-32 weeks of gestation (n=11, 15%). Distending pressure measured in the pharynx is dependent on the flow rate used and weight of the infant.

There was a significant positive relation between birth weight and success rate of HHHFNC as post extubation at flow rate 3 l\min. as showed in subgroup A with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.

Table 5. Causes of extubation failure after using HHHFNC in the main studied group (n = 30) showing

Causes of extubation failure on HHHFNC	Group A (n = 15)		Group B (n = 15)		χ^2	p
	No.	%	No.	%		
Apnea	3	20.0	3	20.0	0.0	FEp=1.000
Collapse	7	46.7	10	66.7	1.222	0.269
Increased FiO$_2$	3	20.0	5	33.3	0.682	FEp=0.682
Sepsis	3	20.0	8	53.3	3.589	0.058
Increased work of breathing	10	66.7	10	66.7	0.0	1.000

- There was no significant difference between the 2 subgroups A & B as regard all causes of extubation failure after using HHHFNC including: apnea, collapse, increased FiO2, sepsis and increased work of breathing.; χ^2: Chi square test; FE: Fisher Exact; U: Mann Whitney test; t: Student t-test; p: p value for comparing between the studied groups. *: Statistically significant at p ≤ 0.05. Group A: extubated to HHHFNC at flow rate 3 L\min. Group B: extubated to HHHFNC at flow rate 6 L\min

Table 6. The conventional mechanical ventilator parameters at time of extubation & the outcomes in the main studied group (n=30) showing

	Group A (n = 15)		Group B (n = 15)		Test of Sig.	p
	No.	%	No.	%		
PIP on extubation						
Min. – Max.	10.0 – 15.0		10.0 – 15.0		t= 1.803	0.082
Mean ± SD.	11.67 ± 1.76		12.87 ± 1.88			
Median (IQR)	11.0 (10.0 – 12.0)		12.0 (11.0 – 15.0)			
Rate on extubation						
Min. – Max.	15.0 – 25.0		15.0 – 25.0		t= 1.521	0.139
Mean ± SD.	17.53 ± 3.66		19.80 ± 4.46			
Median (IQR)	15.0 (15.0 – 20.0)		20.0 (15.0 – 25.0)			
PEEP on extubation						
Min. – Max.	4.0 – 5.0		4.0 – 5.0		t= 0.418	0.679
Mean ± SD.	4.73 ± 0.46		4.80 ± 0.41			
Median (IQR)	5.0 (4.50 – 5.0)		5.0 (5.0 – 5.0)			
FIO$_2$ on extubation						
Min. – Max.	21.0 – 30.0		21.0 – 30.0		t= 1.132	0.267
Mean ± SD.	23.27 ± 3.26		24.80 ± 4.11			
Median (IQR)	21.0 (21.0 – 25.0)		25.0 (21.0 – 30.0)			
BPD						
Negative	13	86.7	8	53.3	χ^2= 3.968	FEp=
Positive	2	13.3	7	46.7		0.109
Pneumothorax						
Negative	13	86.7	12	80.0	χ^2= 0.240	FEp=1.000
Positive	2	13.3	3	20.0		
IVH ≥ II	2	13.3	5	33.3	χ^2= 1.677	FEp=0.390
Pulmonary hemorrhage						
Negative	14	93.3	13	86.7	χ^2= 0.370	FEp=
Positive	1	6.7	2	13.3		1.000
Death rate						
Survived	14	93.3	13	86.7	χ^2= 0.370	FEp=
Died	1	6.7	2	13.3		1.000

- There was no significant difference between the 2 subgroups A & B as regard the mechanical ventilator parameters at time of extubation and the secondary outcomes of HHHFNC including: incidence of BPD, IVH≥II, pneumothorax, pulmonary hemorrhage and death rate. χ^2: Chi square test; FE: Fisher Exact; U: Mann Whitney test; t: Student t-test; p: p value for comparing between the studied groups; *: Statistically significant at p ≤ 0.05; Group A: extubated to HHHFNC at flow rate 3 L\min; Group B: extubated to HHHFNC at flow rate 6 L\min.

Table 7. Relation between gestational age and success rate of HHHFNC as regard its primary outcomes in each subgroup (n = 30) showing

	Success rate	N	Gestational age (weeks)			t	p
			Min. – Max.	Mean ± SD.	Median		
Group A (n = 15)	**Need for Higher flow rate of HHHFNC (3 into 6 l\min.)**						
	Not needed	4	32.0 – 35.0	33.25 ± 1.50	33.0	1.907	0.079
	Needed	11	30.0 – 34.0	31.64 ± 1.43	31.0		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	8	32.0 – 35.0	33.13 ± 1.13	33.0	3.983[*]	0.002[*]
	Needed	7	30.0 – 33.0	30.86 ± 1.07	31.0		
	Need for intubation						
	Not needed	12	30.0 – 35.0	32.50 ± 1.45	32.50	2.488[*]	0.027[*]
	Needed	3	30.0 – 31.0	30.33 ± 0.58	30.0		
Group B (n = 15)	**Need for Higher flow rate of HHHFNC (6 into 8 l\min.)**						
	Not needed	9	30.0 – 35.0	32.11 ± 1.69	32.0	1.368	0.195
	Needed	6	30.0 – 33.0	31.0 ± 1.26	30.50		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	6	30.0 – 35.0	31.83 ± 2.23	31.0	0.282	0.786
	Needed	9	30.0 – 33.0	31.56 ± 1.13	32.0		
	Need for intubation						
	Not needed	11	30.0 – 35.0	32.09 ± 1.58	32.0	1.860	0.086
	Needed	4	30.0 – 32.0	30.50 ± 1.0	30.0		

- There was a significant positive relation between gestational age and success rate of HHHFNC as post extubation at flow rate 3 l\min. as showed in subgroup A with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC and not needed for reintubation.
- There was no significant relation between gestational age and the HHHFNC outcomes as need for higher flow rate of HHHFNC or need for intubation in subgroup A.
- There was no significant relation between gestational age and the HHHFNC outcomes as need for higher flow rate of HHHFNC, need for n CPAP or NIMV after failure of the higher flow rate or need for intubation in subgroup B.

χ^2: Chi square test;
FE: Fisher Exact
U: Mann Whitney test;
t: Student t-test
p: p value for comparing between the studied groups.
*: Statistically significant at $p \leq 0.05$.
Group A: extubated to HHHFNC at flow rate 3 L\min.
Group B: extubated to HHHFNC at flow rate 6 L\min.

There was a significant positive relation between birth weight and success rate of HHHFNC as post extubation at flow rate 6 l\min. as showed in subgroup B with cases who were not needed for higher flow rate of HHHFNC.

This comes in agreement with, Manley, at al. [10], who enrolled 152 very preterm infants to receive treatment with high-flow nasal cannula (5 to 6 L\min) after extubation.

63 of the infants had a gestational age of less than 26 weeks, but the study was not powered to evaluate the efficacy or safety of HFNC in the extremely preterm subgroup. The failure rate was very high among these infants, regardless of the assigned treatment. Given this finding, it should be cautious before using HFNC as first-line respiratory support in extremely preterm infants after extubation.

Table 8. Relation between birth weight and success rate of HHHFNC as regard its primary outcomes in each subgroup (n = 30) showing

	Success rate	N	Weight (kgs)			t	p
			Min. – Max.	Mean ± SD.	Median		
Group A (n = 15)	**Need for Higher flow rate of HHHFNC (3 into 6 l\min.)**						
	Not needed	4	1.70 – 2.00	1.85 ± 0.13	1.85	0.752	0.466
	Needed	11	1.40 – 2.40	1.75 ± 0.26	1.70		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	8	1.70 – 2.40	1.90 ± 0.23	1.85	2.690[*]	0.019[*]
	Needed	7	1.40 – 1.80	1.63 ± 0.15	1.60		
	Need for intubation						
	Not needed	12	1.60 – 2.40	1.83 ± 0.22	1.80	1.849	0.087
	Needed	3	1.40 – 1.80	1.57 ± 0.21	1.50		
Group B (n = 15)	**Need for Higher flow rate of HHHFNC (6 into 8 l\min.)**						
	Not needed	9	1.40 – 2.40	1.87 ± 0.33	1.80	3.161[*]	0.008[*]
	Needed	6	1.30 – 1.60	1.42 ± 0.12	1.40		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	6	1.60 – 2.40	1.97 ± 0.35	1.85	2.992[*]	0.019[*]
	Needed	9	1.30 – 1.80	1.50 ± 0.19	1.40		
	Need for intubation						
	Not needed	11	1.30 – 2.40	1.77 ± 0.36	1.70	1.702	0.113
	Needed	4	1.30 – 1.60	1.45 ± 0.13	1.45		

- *There was a significant positive relation between birth weight and success rate of HHHFNC as post extubation at flow rate 3 l\min. as showed in subgroup A with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.*
- *There was no significant relation between birth weight and the HHHFNC outcomes as need for higher flow rate of HHHFNC or need for intubation in subgroup A.*
- *There was a significant positive relation between birth weight and success rate of HHHFNC as post extubation at flow rate 6 l\min. as showed in subgroup B with cases who were not needed for higher flow rate of HHHFNC.*
- *There was significant positive relation between birth weight and not needing for n CPAP or NIMV after failure of higher flow of HHHFNC as showed in subgroup B.*
- *There was no significant relation between birth weight and the need for intubation as HHHFNC outcome in subgroup B.*

χ^2: *Chi square test; FE: Fisher Exact; U: Mann Whitney test; t: Student t-test*
p: p value for comparing between the studied groups.; *: Statistically significant at $p \le 0.05$.
Group A: extubated to HHHFNC at flow rate 3 L\min.
Group B: extubated to HHHFNC at flow rate 6 L\min.

5. CONCLUSION

Our study concluded that:

- HHHFNC use is noninferior to other forms of non-invasive respiratory support in preterm infants with respiratory distress for prevention of extubation failure.
- HHHFNC showed lesser complications on either flow rates 3 or 6 l\min. as regard nasal trauma, pneumothorax, pulmonary hemorrhage, IVH≥ II, NEC≥ II, PDA and death.
- There were better outcomes for the use of HHHFNC with higher gestational age and birth weight as post extubation support at either flow rates 3 or 6 L/min.

CONSENT AND ETHICAL APPROVAL

The approval from the ethical committee of Tanta University and after written parental consents before the enrollment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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