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The Effectiveness of the Heated Humidified High Flow Nasal Cannula as an Initial Noninvasive Respiratory Support for Preterm Infants Suffering from Respiratory Distress

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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.

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ABSTRACT

Aims: to compare the efficacy and safety of the heated humidified high-flow nasal cannula as a noninvasive respiratory support for the initial management of respiratory distress in preterm infants ≥ 30 weeks gestation with birth weight ≥ 1300 g at different flow rates (3 L/min and 6 L/min) on admission.
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 neonates, with gestational ages ranged between 30 to 36 weeks and birth weight ≥ 1300 g, were randomized to receive HHHFNC at either flow rate 3 or 6 L\min as an initial respiratory support. Primary outcomes included: 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 intubation.

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Secondary outcomes included: rate of deaths at any time after randomization, the total duration of all types of oxygen support and incidence of neonatal morbidities such as nasal trauma, 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).

Results: the incidence of the need for higher flow rate of HHHFNC (n=11, 36.6%) , the need for n CPAP or NIMV after failure of higher flow rate of HHHFNC (n=11, 36.6%), the need for intubation & MV (n=1, 3.3%), the incidence of nasal trauma (n=7, 23.3%), BPD (n=0) , IVH ≥ II (n=0), NEC ≥II (n=0), pneumothorax (n=0) , the median duration of hospitalization =10 days (7-15), the median duration of all oxygen support = 6.5 days (6-7). The failure rate was 11 out of 30 infants (36.6%), no deaths or pulmonary haemorrhage.

Conclusion: HHHFNC use shows similar rates of efficacy to other forms of noninvasive respiratory support in preterm infants with respiratory distress for initial respiratory support with lesser complications. There were better outcomes with higher gestational age and birth weight at either flow rates 3 or 6 L/min.

Keywords: Heated humidified high flow nasal cannula; noninvasive; initial support; preterm; respiratory distress.

1. INTRODUCTION

Preterm is live born infant delivered before 37 weeks from the first day of the last menstrual period according to world health organization [1].

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 [2].

Worldwide, the preterm birth rate is estimated to be about 11 percent ranging from 5 percent (parts of Europe) to 18 percent (parts of Africa) and about 15 million children are born preterm each year (ranging from 12 to 18 millions) [3,4].

In Egypt, Preterm birth rate in 2010 was 7.3(%) and was ranked number 152 among world countries [5].

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 [3].

Preterm neonates can develop many complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia (BPD), neonatal sepsis, symptomatic patent ductus arteriosus, retinopathy of prematurity and hyperbilirubinemia [6].

RDS is considered the major reason for increased mortality and morbidity among infants. It occurs in infants whose lungs have not yet fully developed. It can also be due to genetic problems with lung development. Most cases of RDS occur in babies born before 37 weeks [7].

Respiratory support is being achieved more frequently with nasal continuous positive airway pressure (nCPAP) and other less invasive approaches, such as the technique of intubation, surfactant, and extubation (INSURE) [8].

The non-invasive respiratory support, including nCPAP, was shown to be effective in treating infants in the initial phase of respiratory distress. The heated humidified high-flow nasal cannula is frequently used as an alternative mode of noninvasive respiratory support in the neonatal intensive care unit. Because it has a simpler interface with the infant and smaller prongs than nCPAP, the cannula is perceived as easier to use, more comfortable for the infant, and advantageous for mother–infant bonding [9].

Recent Cochrane review of HHHFNC use in preterm infants concluded that it is effective as other forms of non-invasive respiratory support in preterm infants for preventing treatment failure, death and chronic lung disease [10].

It 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 [11].

It has been used as a respiratory support for various purposes including apnoea of prematurity [12], primary respiratory support in RDS [13], CPAP weaning [14] and post extubation [15].

Also, neonatal HHHFNC is increasingly being applied in other clinical areas including during neonatal transport and for initial delivery room stabilization of premature infants [16, 17,18].

2. MATERIAL AND METHODS

We enrolled total 45 preterm neonates after delivery in this study (15 preterm infants were excluded due to major congenital malformations, or congenital heart disease), they were admitted in the Neonatal Intensive Care Unit (NICU), Pediatrics department, Tanta University Hospitals, over one-year period, from December 2018 to December 2019, after the approval from the ethical committee of Tanta University and after written parental consents before the enrollment.

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 were suffering from mild to moderate respiratory distress on admission, were randomized to receive HHHFNC (Fisher & Paykel Optiflow System, Healthcare, Auckland, New Zealand) as an initial respiratory support [19].
- This group was sub classified into subgroup **A** started initially at flow rate **3 L\min.** and subgroup **B** started initially at flow rate 6 L\min.

2.1 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.

2.2 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.
- Preterm infants who required intubation and mechanical ventilation after delivery.

2.3 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) [19], 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.

2.4 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 [20].

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

I. Respiratory acidosis ($PaCO_2$ > 60 mmHg with pH < 7.25 at maximum setting of the allocated device [flow rate 7-8 L/min]), hypoxia (FiO_2 > 0.4 to maintain SpO_2 88 to 94%) [20].
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 [20].

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.

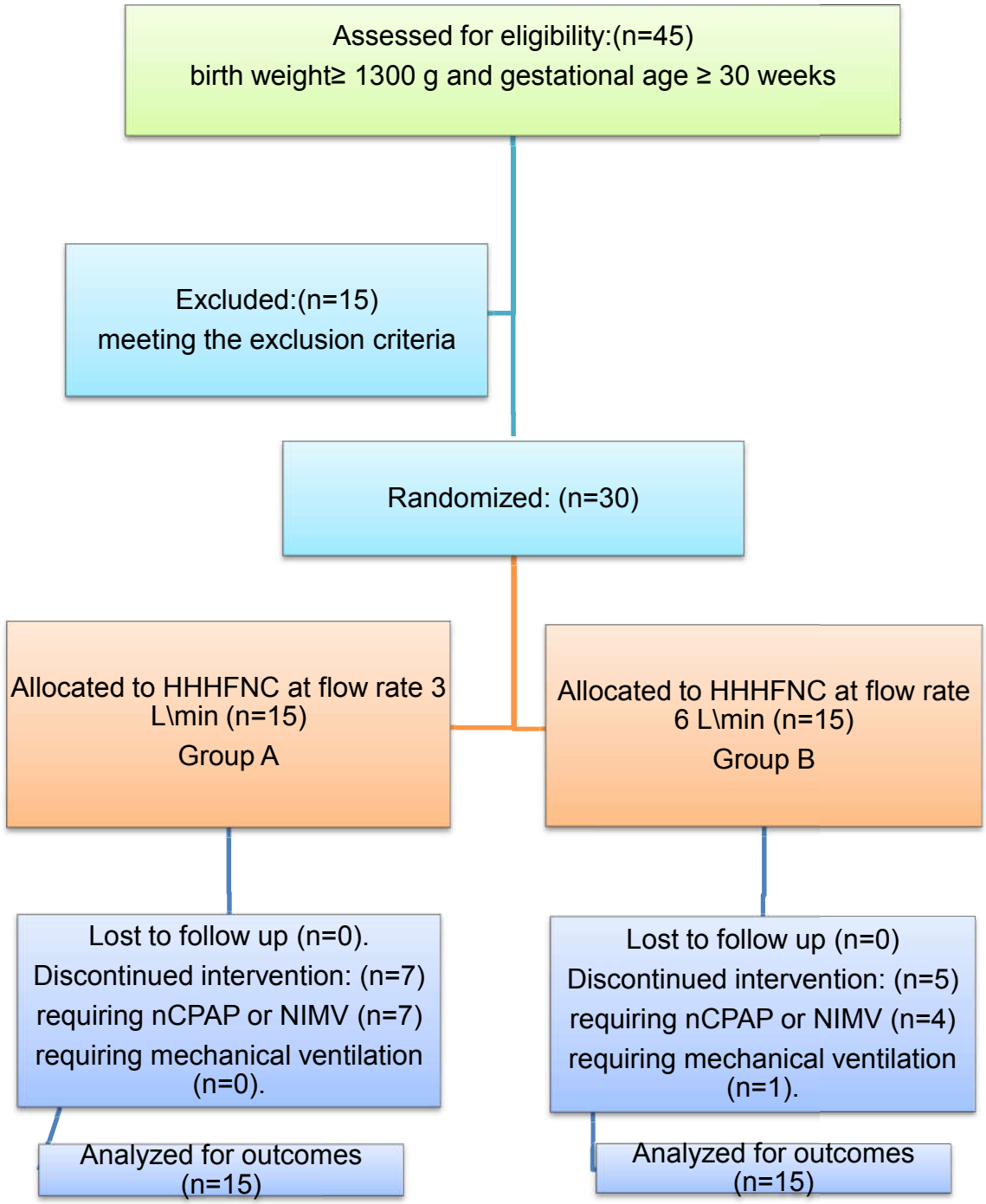

Fig. 1. Participants CONSORT flow diagram

The HHHFNC outcomes:

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 intubation.

Secondary outcomes:

1. Rate of deaths at any time after randomization.
2. The total duration of all types of oxygen support.
3. Incidence of neonatal morbidities such as nasal trauma, 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).

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.

2.5 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.

4. RESULTS

- There was no significant difference between the two studied subgroups A & B as regard sex, gestational age, mode of delivery & age of start of HHHFNC.

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

Ponderal Index = 100 x Weight (grams) / Height^3 (cm).

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

	Group A (n = 15)		**Group B (n = 15)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Sex						
Male	11	73.3	8	53.3	χ^2=	0.256
Female	4	26.7	7	46.7	1.292	
Gestational age (weeks)						
Min. – Max.	31.0 – 36.0		30.0 – 35.0		t=	0.435
Mean ± SD.	33.40 ± 1.40		33.0 ± 1.36		0.792	
Median (IQR)	33.0 (32.50 –34.50)		33.0 (32.50 – 34.0)			
Mode of delivery						
NVD	3	20.0	6	40.0	χ^2=	FEp=
C.S	12	80.0	9	60.0	1.429	0.427
Age of start of HHHFNC (days)						
Min. – Max.	1.0 – 3.0		1.0 – 3.0		U=	0.902
Mean ± SD.	1.60 ± 0.83		1.60 ± 0.91		109.50	
Median (IQR)	1.0 (1.0 – 2.0)		1.0 (1.0 – 2.50)			

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.

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.	1.60 – 2.80	1.30 – 2.50	**1.297**	**0.205**
Mean ± SD.	2.18 ± 0.37	2.0 ± 0.39		
Median (IQR)	2.20 (1.80 – 2.50)	2.20 (1.65 – 2.30)		
Length (cms)				
Min. – Max.	40.0 – 47.0	40.0 – 45.0	**1.635**	**0.113**
Mean ± SD.	43.53 ± 2.17	42.33 ± 1.84		
Median (IQR)	44.0 (42.0 – 45.0)	43.0 (40.50 – 44.0)		
H.C. (cms)				
Min. – Max.	30.0 – 32.0	29.0 – 32.0	**1.080**	**0.289**
Mean ± SD.	30.90 ± 0.81	30.60 ± 0.71		
Median (IQR)	31.0 (30.0 – 31.50)	31.0 (30.0 – 31.0)		
Ponderal index				
Min. – Max.	2.20 – 3.0	2.0 – 3.40	**0.113**	**0.911**
Mean ± SD.	2.59 ± 0.26	2.57 ± 0.38		
Median (IQR)	2.60 (2.40 – 2.75)	2.50 (2.30 – 2.75)		

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.
H.C: Head circumference.

Table 3. Antenatal Risk Factors in Group 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	6	40.0	0.536	0.464
Pre-eclampsia, eclampsia	1	6.7	8	53.3	7.778*	^{FE}P=0.014*
Multiple pregnancies	3	20.0	1	6.7	1.154	^{FE}P=0.598
Abruptio placenta, placenta accrete	1	6.7	1	6.7	0.000	^{FE}P=1.000
Negative	4	26.7	0	0.0	4.615	^{FE}P=0.100
Others: UTI, chorioamnionitis & IDM	1	6.7	2	13.3	0.370	^{FE}P=0.100

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.
PROM: Premature rupture of membranes.
UTI: Urinary tract infections.
IDM: Infant of diabetic mother.

- There was a statistically significant increase as regard number of cases with pre-eclampsia and eclampsia in subgroup B as compared to subgroup A.
- There was no significant difference between the two subgroups A & B as regard antenatal risk factors as PROM, multiple pregnancies, abruptio placenta, others as UTI, chorioamnionitis and IDM.
- There was no significant difference between the 2 subgroups A & B as regard all 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, incidence of nasal trauma, duration of antibiotics, hospitalization & all oxygen support.

Table 4. Follow up data of Subgroup 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	7	46.7	12	80.0	χ^2=	0.058
Needed	8	53.3	3	20.0	3.589	
Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
Not needed	8	53.3	11	73.3	χ^2=	0.256
Needed	7	46.7	4	26.7	1.292	
Need for intubation						
Not needed	15	100.0	14	93.3	χ^2=	^{FE}p=
Needed	0	0.0	1	6.7	1.034	1.000
Nasal trauma						
None	12	80.0	11	73.3	χ^2=	^{FE}p=
Nasal trauma	3	20.0	4	26.7	0.186	1.000
Antibiotics duration (days)						
Min. – Max.	7.0 – 15.0		7.0 – 21.0		U=	0.967
Mean ± SD.	10.80 ± 3.88		11.07 ± 3.90		111.50	
Median (IQR)	10.0 (7.0 – 15.0)		10.0 (8.50 – 14.0)			
Duration of hospitalization (days)						
Min. – Max.	7.0 – 15.0		7.0 – 21.0		U=	0.967
Mean ± SD.	10.80 ± 3.88		11.07 ± 3.90		111.50	
Median (IQR)	10.0(7.0 – 15.0)		10.0(8.50 – 14.0)			
Total duration of all O_2 support (days)						
Min. – Max.	4.0 – 11.0		4.0 – 15.0		t=	0.646
Mean ± SD.	7.67 ± 2.38		7.20 ± 3.08		0.465	
Median (IQR)	7.0 (6.0 – 10.0)		6.0 (5.0 – 9.0)			

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.
HHHFNC: Heated humidified high-flow nasal cannula.
N CPAP: Nasal continuous positive airway pressure.
NIMV: noninvasive mechanical ventilation.

- There was significant positive relation between gestational age and success rate of HHHFNC as initial support 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 significant positive relation between gestational age and success rate of HHHFNC as initial support at flow rate 6 l\min. as showed in subgroup B with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.
- There was significant positive relation between birth weight and not needing for higher flow rate of HHHFNC as showed in subgroup A at flow rate 3 l\min.
- There was significant positive relation between birth weight and success rate of HHHFNC as initial support 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 significant positive relation between birth weight and success rate of HHHFNC as initial support at flow rate 6

l\min. as showed in subgroup B with higher number of cases who were not needed for higher flow rate of HHHFNC and not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.

- There was no significant relation between birth weight and need for intubation as HHHFNC outcome in the main studied group.

4. DISCUSSION

In this present study, in the main studied group (HHHFNC used as an initial respiratory support), as regard the demographic data, anthropometric measurements, antenatal risk factors and HHHFNC outcomes, there was no significant difference between both low and high flow rates subgroups A & B except for incidence of preeclampsia and eclampsia in B (n=8, 53.3%) was higher than in A (n=1, 6.7%). We enrolled 30 preterm infants in with mean GA 33 weeks (32.5-34) & mean BW 2200 g (1800-2500). Resulted in the followings: the incidence of the need for higher flow rate of HHHFNC (n=11, 36.6%), the need for n CPAP or NIMV after failure of higher flow rate of HHHFNC (n=11, 36.6%), the need for intubation & MV (n=1, 3.3%), the incidence of

Table 5. 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	**7**	33.0 – 35.0	34.14 ± 0.90	34.0	2.151	0.051
	Needed	**8**	31.0 – 36.0	32.75 ± 1.49	32.50		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	**8**	33.0 – 36.0	34.37 ± 1.06	34.50	4.329*	0.001*
	Needed	**7**	31.0 – 33.0	32.29 ± 0.76	32.0		
	Need for intubation						
	Not needed	**15**	31.0 – 36.0	33.40 ± 1.40	33.0	–	–
	Needed	**0**	–	–	–		
Group B (n = 15)	**Need for Higher flow rate of HHHFNC (6 into 8 l\min.)**						
	Not needed	**12**	30.0 – 35.0	33.33 ± 1.30	33.0	2.117	0.054
	Needed	**3**	31.0 – 32.0	31.67 ± 0.58	32.0		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	**11**	33.0 – 35.0	33.64 ± 0.81	33.0	4.833*	<0.001*
	Needed	**4**	30.0 – 32.0	31.25 ± 0.96	31.50		
	Need for intubation						
	Not needed	**14**	30.0 – 35.0	33.07 ± 1.38	33.0	–	–
	Needed	**1**		32.0#			

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.
HHHFNC: Heated humidified high-flow nasal cannula.
N CPAP: Nasal continuous positive airway pressure.
NIMV: noninvasive mechanical ventilation.

Table 6. 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	**7**	2.20 – 2.80	2.47 ± 0.20	2.50	4.131*	0.001*
	Needed	**8**	1.60 – 2.50	1.93 ± 0.30	1.80		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	**8**	2.20 – 2.80	2.48 ± 0.18	2.50	6.409*	<0.001*
	Needed	**7**	1.60 – 2.20	1.84 ± 0.20	1.80		
	Need for intubation						
	Not needed	**15**	1.60 – 2.80	2.18 ± 0.37	2.20	–	–
	Needed	**0**	–	–	–		
Group B (n = 15)	**Need for Higher flow rate of HHHFNC (6 into 8 l\min.)**						
	Not needed	**12**	1.30 – 2.50	2.13 ± 0.32	2.20	3.266*	0.006*
	Needed	**3**	1.50 – 1.50	1.50 ± 0.00	1.50		
	Need for n CPAP or NIMV after failure of higher flow rate of HHHFNC						
	Not needed	**11**	1.80 – 2.50	2.20 ± 0.20	2.20	7.063*	<0.001*
	Needed	**4**	1.30 – 1.50	1.45 ± 0.10	1.50		
	Need for intubation						
	Not needed	**14**	1.30 – 2.50	2.04 ± 0.37	2.20	–	–
	Needed	**1**		1.50#			

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
Group A: Initial support by HHHFNC at flow rate 3 L\min.
Group B: Initial support by HHHFNC at flow rate 6 L\min.
HHHFNC: Heated humidified high-flow nasal cannula.
N CPAP: Nasal continuous positive airway pressure.
NIMV: noninvasive mechanical ventilation.

nasal trauma (n=7, 23.3%), BPD (n=0) , IVH ≥ II (n=0), NEC ≥ II (n=0), pneumothorax (n=0) , the median duration of hospitalization =10 days (7-15), the median duration of all oxygen support = 6.5 days (6-7). The cases who needed for n CPAP or NIMV, were changed into higher flow rate first and the case who needed for intubation, was first put on n CPAP or NIMV so failure rate was 11 out of 30 infants (36.6%), no deaths or pulmonary haemorrhage.

This comes in comparison with Shin, et al., 2017 [20], who enrolled 42 preterm infants, were randomized to HHFNC as a primary support when they showed respiratory distress in < 24 hours of age, using the Optiflow system as our study, at the same flow rates, the same weaning criteria from HFNC and the same criteria of treatment failure (intubation). Preterm infants who needed invasive respiratory supports were excluded unlike our study and, they compared the HFNC group to another n CPAP group. The HFNC group, with similar mean GA (32.5±1.5 weeks) and BW (2058±371 g), showed higher failure rate (16%), less need for n CPAP or NIMV (3%), more need for intubation (13%), higher incidence of BPD (n=1, 2.3%), higher incidence of air leak (n=2, 4.7%), IVH ≥ III (n=0), NEC ≥ II

(n=0), longer mean duration of hospitalization =20 days (15.8-28.3) and longer mean duration of all oxygen support =67 days (40-106.8). These differences may be due to the different clinical decisions and rescue treatment.

While in comparison with Sharma, et al., 2019 [21], who enrolled 50 preterm infants with mild to moderate respiratory distress were randomized to HHHFNC as a primary respiratory support within the first 6 h of birth, with smaller mean GA (31.77± 2.21 weeks) and BW (1762 ± 493.5 g), showed higher failure rate 6 out of 50 infants (12%) who needed for intubation and MV, less incidence of nasal trauma (11.4%) and shorter mean duration of total oxygen supplementation =3.48 days. Their study differed from ours in the used devices, the flow rates, the primary outcomes, the weaning protocol, and the rescue treatment.

Dimirel, et al., 2019 [22], who used the HFNC as a first line respiratory support for preterm infants who had spontaneous respiration after admission initially at flow rate 6 L\min and increasing maximally into 8 L\min. They followed the same weaning protocol from HFNC and the same extubation criteria. They enrolled 53 preterm infants with smaller mean GA (31.2±2.3 weeks) and BW (1570±455 g). They found higher intubation (treatment failure) rate (n=5, 9.4%), higher incidence of BPD (n=4, 7.5%), IVH ≥ II (n=2, 3.7%), NEC ≥II (n=1, 1.8%), pneumothorax (n=2, 3.7%), longer median duration of hospitalization =27 days and shorter median duration of all oxygen support = 3 days. They differed from us in the used Vapotherm system and the clinical decisions.

Murki, et al., 2018 [23], who enrolled 133 preterm infants with respiratory distress using HFNC as a primary respiratory support with initial flow rate 5 L\min and increased gradually to the maximal flow rate 7 L\min, with smaller mean GA 31.8±1.9 weeks and BW 1632±431g. They used the same Optiflow system, followed the same treatment failure criteria and the same outcomes. They found lower treatment failure rate within 72 h (n= 35, 26.3%), shorter duration of oxygen support (6.7±4.125 days), higher incidence of nasal trauma (n=7, 5.3%), pneumothorax (n=0), IVH ≥III (n=0), higher incidence of NEC ≥II (n=2, 1.5%), longer duration of hospitalization (18±13 days) and higher death rate (n=4, 3%). Their study differed in the larger numbers included with wider range of GA and BW and also in the clinical rescue decisions.

Manley, et al., 2018 [24], undertook the HIPSTER trial, an international, multicenter, randomized, noninferiority trial in preterm infants born at 28-36 weeks of gestation that used HFNC 6-8 L/min as primary respiratory support for early respiratory distress. All 278 infants in the HFNC group of HIPSTER were included. The mean GA and BW were (32.0 ± 2.1 weeks) and (1737 ± 580 g), and 140 infants (50.4%) were born at< 32 weeks. Caffeine was administered to 109 infants (39.2%) in the first 24 hours of life. The primary outcome was treatment failure within 72 hours after randomization. 71 infants (25.5%) had treatment failure of lower rate compared to our study. In that analysis, when the 30/30 rule was applied: 'infants with both a GA of ≥30 weeks and an early (<2 hours of age) FiO2 <0.30 are more likely to be successfully treated with HFNC and avoid intubation than infants born <30 weeks of gestation or with an early FiO2 ≥ 0.30, or both', about 84% of infants were successfully treated, about 16% required CPAP "rescue," and 7% were intubated. The differences might be due to the larger numbers included with wider range of GA and smaller BW, the used devices and the different NICUs' protocols.

Zheng, et al., 2017 [25], who enrolled 65 preterm infants, with mild to moderate RDS requiring initial noninvasive respiratory support; were applied to the HHHFNC, with smaller GA (31.9±1.7 weeks), BW (1754±299 g). They used the Optiflow and the Vapotherm systems at flow rates 6-8 L\min. They followed the same intubation criteria. Their results showed higher need for intubation (treatment failure) within 7 days (n=13, 20%) unlike ours, higher incidence of BPD (n=6, 9.2%), higher incidence of IVH ≥III (n=3, 4.6%), same incidence of nasal trauma (n=14, 21.5%), air leak (n=2, 3.1%), longer mean duration of hospitalization =30.5 days (14-55) and death rate (n=1, 1.5%). These differences due to the different observational cross-sectional study, used devices, flow rates, protocols, defined primary outcome and decisions.

Lavizzari, et al. 2016 [26], who enrolled 158 preterm infants with mild to moderate RDS, were randomly applied to the HHFNC as a primary support, with mean GA (33.1±1.9 weeks), BW (1968±581 g). They used the Vapotherm system at flow rates 4-6 L\min, followed the same extubation criteria but different intubation indication and weaning criteria from the HHFNC. Their results showed higher incidence of need for MV within 72 h (n=17, 10.8%), higher incidence of BPD (n=7, 4.4%), higher incidence of IVH ≥III

(n=6, 3.8%), higher incidence of air leak (n=3, 1.9%), higher incidence of NEC ≥II (n=1, 0.6%), mean duration of total oxygen support =7.5 days, longer mean duration of hospitalization =20 days (11-35).

Kugelman, et al., 2015 [13], who enrolled 38 preterm infants, randomized to HHHFNC (1 – 5 L\min.) as a primary support, with mean GA 32.5 (27.5-34.7 weeks) and mean BW (1759± 488 g), showed incidence of need for higher flow rate from 3 L\min. (n=14, 36.8%), higher incidence of need for MV (n=11, 28.9%), higher incidence of BPD (n=1, 2.6%), higher incidence of IVH ≥III (n=1, 2.6%), nasal trauma (n=0) , air leak (n=0), NEC ≥II (n=0) , death (n=0) and longer mean duration of hospitalization = 39.5 days (9-113). They differed from us in the pilot study, used Vapotherm at different flow rates and protocols of weaning and intubation.

Lastly, Fleeman, et al., 2019 [27], updated a systematic review and meta-analyses examining the efficacy and safety of HHHFNC compared with standard treatments for preterm infants. The analysis of primary respiratory support included ten RCTs (n =1,676). They found higher intubation rate (n =90\704, 12.8%) compared to our study, higher incidence of BPD (n =27\348, 7.8%), death rate (n =5\717, 0.7%), air leak (n =15\702, 2.1%) and nasal trauma (n =42\578, 7.3%). All the differences are mostly due to the different used devices, flow rates, outcomes, NICUs' protocols, larger ranges of numbers included, GA and BW and the pragmatic clinical decisions.

In this present study, there was a significant positive relation between gestational age and success rate of HHHFNC as initial support 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 a significant positive relation between gestational age and success rate of HHHFNC as initial support at flow rate 6 l\min. as showed in subgroup B with higher number of cases who were not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.

This comes in comparison to, Lavizzari, et al. 2016 [26], who enrolled 158 preterm infants with mild to moderate RDS, were randomly applied to the HHFNC as a primary support. They found that there was no difference in respiratory failure rate in any GA stratum.

While in comparison with, Zheng, et al., 2017 [25], who enrolled 65 preterm infants, with mild to moderate RDS requiring initial noninvasive respiratory support; were applied to the HHHFNC. They found that there were no significant differences in neonates older than 28 weeks of gestational age in the primary outcome: treatment failure within the first 7 days.

While Murki, et al., 2018 [23], who enrolled 133 preterm infants with respiratory distress using HFNC as a primary respiratory support. They found that the risk difference of treatment failure was higher among infants with lower gestation (<32 weeks: 14.7%, ≥32 weeks: 10.1%).

In this present study, there was a significant positive relation between birth weight and success rate of HHHFNC as initial support 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 a significant positive relation between birth weight and success rate of HHHFNC as initial support at flow rate 6 l\min. as showed in subgroup B with higher number of cases who were not needed for higher flow rate of HHHFNC and not needed for n CPAP or NIMV after failure of higher flow of HHHFNC.

There was no significant relation between birth weight and need for intubation as HHHFNC outcome in the main studied group (Initial support).

This comes in agreement with, Yoder, et al., 2013 [28], who enrolled 212 infants, who were randomly assigned to HHHFNC (at flow rates 2 to 8 L\min.) as a primary support, with mean GA (33.5± 3.6 weeks) and BW (2201±816 g). They found that the adjustment for gestation, birth weight, ventilator support, surfactant therapy, and primary diagnosis did not alter the failure rates to identify a significant difference between the study modes for early intubation.

5. CONCLUSION

Our study concluded that:

- HHHFNC use has similar rates of efficacy to other forms of non-invasive respiratory

support in preterm infants with respiratory distress for initial respiratory support.

- 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 an initial respiratory support at either flow rates 3 or 6 L/min.

CONSENT

All authors declare that 'written informed consent was obtained from all the patients' parents for publication of this clinical trial.

ETHICAL APPROVAL

All authors hereby declare that all interventions have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University. Permission number is 32950/2/19.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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