The Effect of Ventilatory Supports on Oxidative Stress Biomarkers in Preterm Respiratory Distress

Original Article

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is the most common respiratory condition in preterm infants, requiring ventilatory support. The challenge lies in optimizing respiratory care while minimizing oxidative stress (OS), with various non-invasive ventilation (NIV) options now available.

Aim of the Work: To compare, humidified high-flow nasal cannula (HHFNC) vs nasal intermittent positive pressure ventilation (NIPPV), in preterm with RDS, by evaluating their effects on OS: serum malondialdehyde (MDA) and total antioxidant capacity (TAC).

Patients and methods: Forty infants (≤35 weeks' gestation) required NIV on first day of life for RDS randomly divided into two groups; HHFNC or NIPPV (*n*=20 each). MDA and TAC were measured at start of NIV and after 24hours.

Results: After 24hours, HHFNC exhibited significantly diminished levels of MDA and TAC than NIPPV (P=0.037 and 0.000, respectively). Non-survivors in HHFNC group recorded significantly higher MDA and TAC levels than survivors ($P < 0.001$). In the NIPPV group, TAC levels were notably higher in patients with BPD versus those without ($P = 0.003$), as well as in those who died compared to those who survived ($P < 0.001$). MDA and TAC levels demonstrated significant positive correlation with length of stay in both groups. Although mortality rate in HHFNC was lower (15%) compared to NIPPV (25%), variation observed was not statistically significant.

Conclusions: HHFNC may offer benefits by reducing OS compared to NIPPV.

Key Words: Non-invasive ventilatory supports, oxidative stress biomarkers, respiratory distress syndrome.

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INTRODUCTION

Respiratory distress syndrome (RDS) is the leading respiratory problem in preterm neonates, frequently demanding respiratory intervention. Research have identified that different ventilation approaches modify its pathological and clinical progression[1].

While poorly developed airways, low surfactant levels, and weak respiratory effort are recognized as key factors for the pathophysiology of RDS, the potential role of oxidative stress (OS) is also being accused of contributing to this pulmonary injury[2].

Prenatally, the fetus is in a state of relatively low oxygen. However, promptly after delivery, the lungs expand and oxygen delivery to tissues doubles, triggering a physiological OS response[3]. Unfortunately, many preterm babies require supplemental oxygen during resuscitation at birth. This increase in oxygen leads to a surge in reactive oxygen species (ROS), overwhelming the underdeveloped antioxidant defenses of these neonates. This imbalance leads to cellular injury to proteins, lipids, and nucleic acids, ultimately contributing to the onset of RDS[2].

Research has proved that numerous mechanical ventilation strategies can induce or reinforce systemic inflammatory reactions, and local inflammation cascades and remodeling in the premature lung, stimulating ventilator-induced lung injury[4], and might significantly influence long-term respiratory outcomes.

Several ventilation modes have been explored to mitigate harm and enhance outcomes, with the ideal approach

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being to avoid invasive mechanical ventilation whenever possible. However, even less invasive ventilation methods can still have detrimental effects by generating ROS and causing tissue damage[5]. Thus, we aimed to compare HHFNC vs nasal intermittent positive pressure ventilation (NIPPV), in preterm infants with RDS, focusing on their impact on OS markers serum malondialdehyde (MDA) and serum total antioxidant capacity (TAC) assessed at the onset of NIV and again 24 hours later.

PATIENTS AND METHODS

This prospective randomized exploratory cohort study, conducted at the Neonatal Intensive Care Unit (NICU) of Ain Shams University Hospital, took place between December 2022 and June 2023. Consent was obtained from the newborns' guardians.

Forty preterm infants ≤ 35 weeks' gestation randomly assigned to HHFNC or NIPPV on day one of life for RDS. RDS was diagnosed based on signs of respiratory distress including tachypnea, grunting, nasal flaring, retractions, cyanosis, and poor perfusion, and was confirmed radiologically via chest X-ray[6].

Neonates with other causes of respiratory distress, chromosomal anomalies, suspected inborn error of metabolism, received surfactant, requiring invasive mechanical ventilation or in need of a surgical procedure were not included.

From the 60 preterm infants assessed for eligibility, 20 were excluded: 14 did not meet the study's criteria, and 6 had parents who did not consent. Thus, 40 preterm babies were included and randomly divided into two groups: the NIPPV group (n = 20) and the HHFNC group (n = 20).

A comprehensive perinatal history was recorded for each included neonate, followed by a detailed clinical assessment. Gestational age was estimated using mother's last menstrual period and verified using the modified Ballard score[7]. Birth weight and APGAR scores at 1 and 5 minutes were documented. Data of enteral feeding progression, length of hospital stay, need for inotropic support, and evidence of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and mortality were documented. All patients received routine care as per our NICU guidelines.

Radiological investigation

Chest x-ray was done on admission for RDS diagnosis and excluding other causes of respiratory distress.

Laboratory analysis

Complete blood picture (CBC): was done on Sysmex X-N-100SA-01

C- reactive protein (CRP): was done on Cobas6000 series-C501

Venous blood gases: was done on ABL800

All were recorded on admission and 72 hours later.

Blood cultures were done on admission.

MDA and TAC were done on day one of NIV and repeated after 24 hours.

Sample collection and storage

Under complete aseptic technique 2ml venous blood was withdrawn by venipuncture from each participant on day one of NIV and repeated after 24 hours. A serum separator tube was used and allowed samples to clot for two hours at room temperature or overnight at 4^{o}C before centrifugation for 20 minutes at approximately 1,000×g.

ELISA for Malondialdehyde and total antioxidant capacity: This assay employs the competitive inhibition enzyme immunoassay technique. A monoclonal antibody specific to malondialdehyde has been pre-coated onto a microplate. A competitive inhibition reaction is launched between biotin labeled malondialdehyde and unlabeled malondialdehyde (Standards or samples) with the pre-coated antibody specific to malondialdehyde. After incubation the unbound conjugate is washed off. Next, avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. The amount of bound HRP conjugate is reverse proportional to the concentration of malondialdehyde in the sample. After addition of the substrate solution, the intensity of color developed is reverse proportional to the concentration of malondialdehyde in the sample.

As for total antioxidant capacity ELISA was done by Cell Biolabs' OxiSelect™ TAC Assay Kit. Samples are compared to a known concentration of uric acid standard within a 96-well microtiter plate. Samples and standards are diluted with a reaction reagent, and, upon the addition of copper, the reaction proceeds for a few minutes. The reaction is stopped and read with a standard 96-well spectrophotometric microplate reader at 490 nm. Antioxidant capacity is determined by comparison with the uric acid standards.

Primary and secondary outcomes

Primary outcome includes comparison between HHFNC vs NIPPV in preterm with RDS as regards their effect on OS biomarkers MDA and TAC performed once the baby was put on NIV then were repeated after 24 hours later. Secondary outcomes include length of hospital stay, evidence of BPD, NEC, mortality and correlate them with OS biomarkers levels in each group.

Sample size

An exploratory prospective cohort study was conducted that included 40 preterm infants with gestational age ≤35 weeks necessitated ventilatory support (HHFNC or NIPPV) primarily for RDS at NICU for 6 months duration (20/group).

Statistical analysis

Data process involved gathering, reviewing, coding, and entering information into IBM SPSS Statistics software, version 23. Parametric quantitative data were summarized using mean, standard deviation, and range, whereas non-parametric data were summarized with median and interquartile ranges (IQR). Qualitative variables were reported as numbers and percentages. To compare qualitative data within groups, we employed the chi-square test and/or Fisher's exact test. For comparing parametric quantitative data, we used the independent t-test, while the Mann-Whitney test was applied for non-parametric data.

To compare two paired groups with parametric quantitative data, we used the paired t-test. For data with a non-parametric distribution, we employed the Wilcoxon rank test. Pearson correlation coefficients were calculated to evaluate the relationship between two quantitative variables within the same group. A 95% confidence interval was applied, with a 5% margin of error. Statistical significance was determined with a *p-value* of less than 0.05, and a *p-value* of less than 0.01 was considered highly significant.

ETHICAL CONSIDERATION

The study protocol was approved by the Research Ethical Committee of Ain Shams University Hospitals, ID: FMASU 573/2022.

RESULTS

Table 1: The clinical characteristics among preterm neonates in HHFNC vs NIPPV groups.

		HHFNC (*n*=20)	NIPPV (*n*=20)	*P value*
Gestational age, (weeks)	Mean ± SD	32.65 ± 1.9	32.3 ± 1.63	0.535
	Range	29 – 35	29 - 35	
Gender, n	Male (%)	10 (50%)	14 (70%)	0.197
Apgar score at 1st minute	Mean ± SD	5± 1	5 ± 1	0.794
	Range	4 – 8	4 – 8	
Apgar score at 5 minutes	Mean ± SD	7 ± 1	7 ± 0	0.303
	Range	6 – 9	6 – 9	
Mode of delivery	Cesarean section	12 (60%)	8 (40%)	0.206
Temperature (°c)	Mean ± SD	36.67 ± 0.31	36.8 ± 0.39	0.232
	Range	36.1 - 37.1	36.1 - 37.8	
Respiratory rate (breath/min)	Mean ± SD	65.8 ± 8.29	65.7 ± 4.57	0.963
	Range	53 – 86	59 - 73	
Heart rate (beat/min)	Mean ± SD	166.25 ± 14.05	170.75 ± 11.31	0.272
	Range	143 – 191	152 - 191	
Systolic blood pressure (mmHg)	Mean ± SD	64.9 ± 5.81	62.3 ± 5.7	0.162
	Range	56 – 74	56 - 74	
Diastolic blood pressure (mmHg)	Mean ± SD	37.25 ± 5.79	34.9 ± 5.55	0.198
	Range	29 – 47	26 - 46	
RDS grading by chest x-ray	Grade 2	9 (45%)	9 (45%)	*0.824
	Grade 3	9 (45%)	10 (50%)	
	Grade 4	2 (10%)	1 (5%)	

HHFNC: humidified high-flow nasal cannula; NIPPV: non-invasive positive pressure ventilation; RDS: respiratory distress syndrome; Test: student t test for numerical parameters and *: chi square test for non-numerical parameters.

(Table 1) shows that there was no significant difference between HHFNC and NIPPV groups as regards clinical characteristics.

Table 2: Oxidative stress markers among preterm neonates in HHFNC vs NIPPV groups.

		HHFNC group	NIPPV group	Test value	*P-value*	Sig.
		No. = 20	No. = 20			
MDA initial	Mean±SD	26.4 ± 7.6	28.1 ± 11.54	-0.550•	0.585	NS
	Range	13 – 41	14 – 62			
MDA after	Mean±SD	11.05 ± 3.98	14.4 ± 5.69	-2.158•	0.037	S
	Range	7 – 23	8 – 34			
*P-value**		<0.001	<0.001			
TAC initial	Mean±SD	33.8 ± 5.85	35.65 ± 14.11	-0.542•	0.591	NS
	Range	23 - 42	14 - 65			
TAC after	Mean±SD	6.35 ± 2.06	16.75 ± 7.56	-5.936•	0.000	HS
	Range	4 - 12	6 – 32			
*P-value**		*P*< 0.001	*P*< 0.001			

HHFNC: humidified high-flow nasal cannula; NIPPV: non-invasive positive pressure ventilation; MDA: malondialdehyde; TAC: total antioxidant capacity *P*>0.05: Non-significant (NS); *P* <0.05: Significant (S); *P* <0.01: Highly significant (HS); •: Independent t-test; *: Paired t-test

(Table 2) shows no considerable difference between the HHFNC and NIPPV groups regarding initial MDA and TAC levels. However, after 24 hours, both groups experienced a significant decrease in MDA and TAC (*P* < 0.001). Additionally, 24 hours later, the HHFNC exhibited significantly lower MDA and TAC levels compared to the NIPPV group (*P*=0.037 and 0.000, respectively).

Table 3: Comparison between HHFNC group and NIPPV group regarding percentage of change of MDA and TAC.

		HHFNC	NIPPV	Test value	*P-value*	Sig.
		No. = 20	No. = 20			
% of reduction of MDA	Mean±SD	60.04 ± 17.52	43.67 ± 23.98	2.272≠	0.023	S
	Range	1.93 – 81.44	0 – 81.37			
	Median (IQR)	62.79 (51 - 70.8)	49.08 (30.28 - 60.33)			
% of reduction of TAC	Mean±SD	80.33 ± 8.2	49.76 ± 22.33	4.788≠	<0.001	HS
	Range	51.66 – 87.03	1.19 – 78.95			
	Median (IQR)	83.43 (77.24 - 85.65)	55.23 (36.62 - 65.69)			

HHFNC: humidified high-flow nasal cannula, NIPPV: non-invasive positive pressure ventilation, MDA: malondialdehyde, TAC: total antioxidant capacity, *P*>0.05: Non-significant (NS); *P* <0.05: Significant (S); *P* <0.01: Highly significant (HS) ≠: Mann-Whitney test

(Table 3) shows that there was statistically significant increase in the percentage of reduction of MDA in HHFNC group than NIPPV group (*P* = 0.023). Also, there was statistically significant increase in the percentage of reduction of TAC in HHFNC group than NIPPV group (*P* <0.001).

Table 4: Laboratory data in HHFNC and NIPPV groups.

			HHFNC (*n*=20)	NIPPV (*n*=20)	*P value*
Initial laboratory tests	Hb (g/dl)	Mean ± SD	16.56 ± 2.63	15.3 ± 1.74	#0.081
	TLC (x109/L)	Mean ± SD	12.54 ± 4.58	11.28 ± 4.84	#0.401
	Platelets (x109/L)	Mean ± SD	279.9 ± 93.6	296.35 ± 112.76	#0.619
	CRP (mg/dl)	Median (IQR)	3.55 (0.98 - 8.83)	8.8 (1.9 - 21.55)	≠0.172
	pH	Mean ± SD	7.31 ± 0.1	7.32 ± 0.11	#0.744
	CO2 (mmHg)	Mean ± SD	39.11 ± 11.64	41.88 ± 11.12	#0.446
	HCO3 (mmol/L)	Mean ± SD	20.44 ± 5.07	21.71 ± 4.64	#0.412
Laboratory test after 72 hours	Hb (g/dl)	Mean ± SD	16.62 ± 2.64	15.32 ± 1.72	#0.072
	TLC (x109/L)	Mean ± SD	8.02 ± 3.17	10.61 ± 4.69	#0.048*
	Platelets (x109/L)	Mean ± SD	278.75 ± 101.21	295.5 ± 102.27	#0.606
	CRP (mg/dl)	Median (IQR)	0.55 (0 – 5.65)	7.8 (0.25 - 19.55)	≠0.041*
	pH	Mean ± SD	7.31 ± 0.1	7.32 ± 0.11	#0.708
	CO2 (mmHg)	Mean ± SD	35.91 ± 11.56	39.68 ± 10.93	#0.296
	HCO3 (mmol/L)	Mean ± SD	16.19 ± 5.6	19.11 ± 4.4	#0.074

Data presented as mean ± SD or median (IQR); HHFNC: humidified high-flow nasal cannula; NIPPV: non-invasive positive pressure ventilation; Hb: hemoglobin; TLC: total leucocyte count; CRP: C-reactive protein; *: significant as *P value* ≤ 0.05; #: student t test; ≠: Mann Whitney test.

(Table 4) demonstrates no appreciable differences between the two groups with respect to initial hemoglobin (Hb), total leukocyte count (TLC), platelets, C-reactive protein (CRP), pH, CO_2, or bicarbonate levels at the initiation of NIV. Likewise, after 72 hours, there were no notable differences in laboratory results between the 2 groups, except for TLC and CRP, which showed a significant rise in the NIPPV patients versus the HHFNC group ($P = 0.048$ and $P = 0.041$, respectively).

Table 5: Clinical outcome of preterm infants with RDS in both studied groups.

		HHFNC (*n*=20)	NIPPV (*n*=20)	*P value*
Duration of hospital days	Mean ± SD	19.55 ± 6.51	26.5 ± 7.23	#0.003*
	Range	10 – 31	11 – 35	
Duration to reach full enteral (days)	Mean ± SD	5.62 ± 1.26	6.85 ± 1.52	≠0.034*
	Range	4 – 7	5 – 9	
Inotropic support		2 (10%)	3 (15%)	≠1.000
NEC, *n* (%)		3 (15%)	5 (25%)	≠0.695
BPD, *n* (%)		1 (5%)	2 (10%)	≠1.000
Mortality, *n* (%)		3 (15%)	5 (25%)	≠0.695

HHFNC: humidified high-flow nasal cannula, NIPPV: non-invasive positive pressure ventilation, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia, *: significant as *P value* ≤ 0.05, #: student t test, ≠: chi square test

As presented in (Table 5), the HHFNC group exhibited a significantly shorter hospital stay and achieved full enteral feeding earlier than the NIPPV group, with *P values* of 0.003 and 0.034, respectively. Additionally, the HHFNC group showed a reduced need for inotropic support, as well as fewer cases of NEC and BPD, although these differences lacked statistical significance. The HHFNC group had a reduced mortality rate of 15% compared to 25% in the NIPPV group, yet this difference did not attain statistical significance.

Table 6: Relation between BPD, mortality and levels of MDA and TAC.

		HHFNC (*n*=20)		NIPPV (*n*=20)	
		MDA	TAC	MDA	TAC
BPD	Yes	23.13	11.8	28.07 ± 8.29	30.73 ± 1.39
	No	10.4 ± 2.86	6.12 ± 1.54	12.8 ± 2.81	15.15 ± 6.12
P value				0.230	0.003*
Mortality	Yes	18.35 ± 4.14	9.7 ± 2.2	19.86 ± 8.74	26.36 ± 4.31
	No	9.74 ± 2.2	5.82 ± 1.26	12.49 ± 2.84	13.49 ± 5.2
P value		<0.001*	<0.001*	0.133	<0.001*

HHFNC: humidified high-flow nasal cannula; NIPPV: non-invasive positive pressure ventilation; MDA: malondialdehyde; TAC: total antioxidant capacity; BPD: bronchopulmonary dysplasia; *: significant as *P value* ≤ 0.05, Student t test

According to (Table 6), in the HHFNC group, non-survivors displayed significantly higher MDA and TAC levels than survivors ($P < 0.001$). In the NIPPV group, TAC levels were notably higher in patients with BPD versus those without ($P = 0.003$), as well as in those who died compared to those who survived ($P < 0.001$). It is worth noting that in the HHFNC group, there is only one patient suffered BPD, with MDA and TAC were higher than the mean in those babies who did not.

Table 7: Correlation between oxidative stress biomarkers levels 24 h after ventilation with length of hospital stay (days).

	HHFNC (*n*=20)				NIPPV (*n*=20)			
	MDA		TAC		MDA		TAC	
	r	P	R	P	r	P	R	P
length of hospital stay	0.487	0.030*	0.597	0.006*	0.534	0.015*	0.585	0.007*

HHFNC: humidified high-flow nasal cannula, NIPPV: non-invasive positive pressure ventilation, MDA: malondialdehyde, TAC: total antioxidant capacity, MV: mechanical ventilation, r: spearman correlation coefficient, *P*: *P value*, *: significant as *P value* ≤ 0.05

In the HHFNC group, a significant positive correlation was found between the length of hospital stay and both MDA and TAC levels ($P = 0.03$ and $P = 0.006$, respectively). Likewise, in the NIPPV group, there was a significant positive association between length of stay and both MDA and TAC levels ($P = 0.015$ and $P = 0.007$, respectively), as shown in (Table 7).

DISCUSSION

RDS is the leading cause of respiratory distress in preterm neonates shortly after birth, necessitating ventilatory support, either invasive or non-invasive, along with supplemental oxygen, with or without surfactant replacement therapy. NIV methods are favored over invasive ventilation because they decrease the likelihood of lung injury and BPD[8].

Premature infants are prone to free radical disorders with significant cellular damage[9]. Besides, OS during the perinatal period is associated with both short-term complications and fetal programming that predisposes individuals to adult diseases[10].

As per our knowledge, this is the first research to compare HHFNC and NIPPV, in preterm patients with RDS, focusing on their effects on OS biomarkers MDA and TAC.

In this study, patients in the HHFNC group had a significantly shorter hospital stay and achieved full enteral feeding earlier than those on NIPPV, with *P values* of 0.003 and 0.034, respectively. Additionally, patients in HHFNC group demonstrated a reduced need for inotropic support, fewer cases of NEC and BPD, and lower mortality rates as compared to the NIPPV patients, though the differences lacked statistical significance.

Kugelman et al.[11] found that although intubation and mechanical ventilation rates were similar between HHFNC and NIPPV as primary respiratory support, the HHFNC group required oxygen supplementation for a longer period.

In 2020, ***Fernandez-Alvarez et al.***[12] conducted a study comparing two HHFNC systems in UK for babies ≤ 28 weeks gestation weaned from NCPAP. The comparison between the Vapotherm vs Optiflow groups revealed no

differences in many morbidities like sepsis, BPD, NEC, IVH, duration of stay, or weight at discharge. While the differences were not statistically significant, infants on Vapotherm required less time on NIV compared to those on Optiflow. The study found a slight benefit in using Vapotherm after birth, though this advantage may lessen in older or more mature infants. Their findings suggest that HHFNC is a safe and effective strategy for weaning off NCPAP, without increasing adverse risks.

For infants > 28 weeks being weaned from mechanical ventilation, HHFNC is generally considered comparable to CPAP, with the additional benefits of easier application. Nonetheless, evidence supporting its use in smaller infants remains scarce ***Wilkinson et al.***[13].

Likewise, ***Hodgson et al.***[14] conducted a systematic review including three trials comparing HHFNC to CPAP and observed no variation in treatment failure or intubation rates. However, most studies focused on infants > 28 weeks' gestation, they determined that there was inadequate evidence to endorse HHFNC as a primary mode or for post-extubation respiratory support in infants born before 28 weeks' gestation.

Conversely, in a large retrospective study of 2,487 extremely preterm neonates, ***Taha et al.***[15] found that HHFNC was linked to a greater incidence of mortality or BPD and a longer hospital stay vs CPAP. Comparably, ***Shi et al.***[16] showed that CPAP is more effective than HHFNC as the initial support for preterm infants with respiratory distress, lowering the likelihood of treatment failure and reducing the necessity for intubation.

Nevertheless, a meta-analysis on HHFNC trials suggested it as the optimal respiratory support method, as long as CPAP and/or NIPPV can be used as a backup. HHFNC's advantages include lower pneumothorax rates, and higher levels of satisfaction among both patients and caregivers[17].

A Cochrane meta-analysis encompassing 10 trials with 1,061 preterm infants found that early use of NIPPV is likely more effective than CPAP in alleviating respiratory failure and minimizing intubation frequency in preterm patients with RDS. There were no significant variations between the two modes in terms of the rates of pneumothorax, BPD, NEC, IVH, or mortality[18].

Comparably, in their study, ***Buyuktiryaki et al.***[19] highlighted that CPAP group had a significantly higher NIV failure rate (29.4%) within the initial 72 hours of life in contrast to both BiPAP (12.9%) and NIPPV (12.4%) groups (P<0.001), whereas BiPAP and NIPPV did not differ significantly (P=0.91).

On the other hand, ***Nath et al.***[20], declared that NIPPV showed higher incidence of failure than CPAP when employed as the initial support method in preterm patients with respiratory distress 62.1% vs 30.1%, respectively (P= 0.003).

Initially, in our study, MDA and TAC levels were comparable between the HHFNC and NIPPV groups. However, after 24 hours, both groups exhibited a significant reduction in these biomarkers (P<0.001), with the HHFNC group showing a notably greater decrease in MDA and TAC compared to the NIPPV group.

Our findings showed a significant positive correlation between hospital stay duration and both MDA and TAC levels after 24 hours of NIV initiation in the HHFNC group, with a similar trend in the NIPPV group. In the HHFNC group, non-survivors had significantly higher MDA and TAC levels than survivors. In the NIPPV group, elevated TAC levels were found in patients with BPD and those who died, while MDA levels showed no significant difference.

In their study ***Elkabany et al.***[21] documented that preterm with RDS exhibited elevated MDA, advanced oxidation protein products (AOPPs), and 8-hydroxy-2-deoxyguanosine (8OHdG) levels on days 0 and 3, while TAC, zinc, and copper levels were significantly decreased relative to control ($p < 0.05$ for all). Furthermore, they realized that MDA, AOPPs, and 8-OHdG levels rose by day 3, whereas TAC and zinc levels dropped on day 3 ($p < 0.001$) for neonates with RDS.

Our results contrasted with theirs, as we found that MDA and TAC after 24 hours of NIV in both groups exhibited a significant reduction (P<0.001). The variation in outcomes might be explained by the older gestational age of our patients, 32.48 ± 1.77 weeks compared to 30.9 ± 1.9 weeks in their study. Moreover, they likely included more severe cases of RDS, given that we excluded patients who required surfactant, while 65% of theirs required.

In this cohort, the reduction in TAC after 24 hours of NIV initiation is likely due to its depletion in response to neutralizing the initial elevated plasma MDA, which aligns with the findings of ***Moustafa et al.***[22], who reported low TAC in umbilical venous blood due to its depletion in addressing high plasma peroxide levels.

Dursun et al.[23] noted that neonates on synchronized intermittent mechanical ventilation (SIMV) and CPAP had considerably higher mean levels of ischemia-modified albumin (IMA), total oxidant status (TOS), and oxidative stress index (OSI = TOS/TAC) during ventilation support versus after it was discontinued (p = 0.001). Mean TAC was significantly lower during ventilation than after its cessation (p = 0.001).

In 2011 study by ***Dizdar et al.***[24] evaluated the oxidant and antioxidant status of preterm babies with RDS. They demonstrated that younger infants had reduced TAC levels, which significantly increased along with the TAC/TOS ratio following surfactant therapy. Infants with lower initial TAC levels required more prolonged respiratory support and had longer hospital stays. A lower TAC/TOS ratio at baseline was linked to increased mortality.

Cavia-Saiz et al.[10] examined changes in OS markers in healthy full-term infants' plasma and urine during the first hours after birth. They observed that, at 48 hours post-birth, blood TAC levels slightly increased while MDA levels decreased compared to cord blood. This aligns with previous findings by ***Stefanov et al.*** who showed OS rise during pregnancy, with greater rise at delivery, followed by a decline[25].

The variations in oxidant/antioxidant levels and discrepancies across studies are likely due to factors such as the timing of the measurements, the type of assays employed, and the highly reactive and transient nature of the ROS being assessed, Additionally, variations in gestational age, the severity of RDS, and differing management guidelines for RDS may also contribute to the divergent results reported in these studies.

This study has some limitations, including the small sample size. Additionally, we did not examine the correlation between oxidative stress markers, MDA and TAC, and the ventilatory settings or the highest fraction of inspired oxygen used during the first 24 hours of NIV. We also did not assess the correlation between these markers and the failure rates of the different NIV modes employed.

CONCLUSION

HHFNC may have advantages in terms of reducing inflammation, oxidative stress and improving clinical outcomes such as shorter hospital stays and faster reach full enteral feed compared to NIPPV in this cohort of preterm neonates with RDS.

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FINANCIAL DISCLOSURE

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CONFLICT OF INTERESTS

There is no conflicts of interest.

CONTRIBUTORS' STATEMENT PAGE

Shaaban HA and Gad TM conceptualized and designed the study.

Shaaban HA contributed to conceptualization and drafted the initial manuscript.

Aly HH and Ramadan MAM supervised data collection, laboratory investigations and analyzed and interpreted the data.

We confirm that this manuscript has not been published elsewhere and is not under consideration by any other journal.

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تأثير التهوية الميكانيكية على عوامل الأكسدة في الضائقة التنفسية لدي الخدج

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الخلفية: متلازمة الضائقة التنفسية هي الحالة التنفسية الأكثر انتشاراً بين الخدج، ويستلزم دعم التنفس الصناعي. لا يزال تحسين دعم الجهاز التنفسي مع تقليل الإجهاد التأكسدي يمثل تحديًا.

الهدف: مقارنة قنية الأنف عالية التدفق المرطبة HHFNC والتهوية الأنفية بالضغط الإيجابي المتقطع NIPPV ، عند الخدج المصابين بمتلازمة الضائقة التنفسية، من خلال تقييم مصل المالونديالدهيد (MDA) والقدرة الكلية لمضادات الأكسدة (TAC).

الطرق: احتاج أربعون رضيعًا (≤٣٥ أسبوعًا) دعم الجهاز التنفسي غير الغازي في اليوم الأول بسبب متلازمة الضائقة التنفسية مقسمين عشوائيًا: HHFNC أو NIPPV (العدد=٢٠ لكل منهما). وقياس MDA وTAC عند بداية NIV وبعد ٢٤ ساعة.

النتائج: بعد ٢٤ ساعة، HHFNC أظهرت مستويات متناقصة بشكل ملحوظ من MDA and TAC مقارنة بـ .NIPPV زاد كلاً من MDA وTAC في مرضي HHFNC الذين توفوا مقارنة بأولئك الذين عاشوا. في حين إرتفعت مستويات TAC بشكل ملحوظ عند مرضى NIPPV الذين عانوا من خلل التنسج القصبي الرئوي أو الوفاة من أولئك الذين لم يعانوا. وجدت علاقة إيجابية بين MDA و TAC و مدة الإقامة في كلا المجموعتين. على الرغم من أن معدل الوفيات في HHFNC كان أقل منNIPPV إلا أن التباين لم يكن ذا دلالة إحصائية.

الاستنتاجات: قد يقدم HHFNC فوائد عن طريق تقليل الإجهاد التأكسدي مقارنةً بـ NIPPV.