Annals of Neonatology

OPEN ACCESS
ISSN: 2636-3596

Original Article

Inhaled Salbutamol Versus Epinephrine in Treatment of Transient Tachypnea of Newborn (TTN): A Randomized Control Trial

Nada M. Ali[1]*, Yasser Abdel-Rahman Ahmed[2], Hosny A. Ahmed[2], Ahmed M. Sayed[3]
DOI: 10.21608/ANJ.2023.239961.1076
***Correspondence:** Department of Pediatrics, Ministry of health, Sohag Government, Egypt
Email: nadamali82@gmail.com

Abstract

Background: One of the most frequent causes of respiratory distress in newborns, particularly in late-preterm and term infants, is transient tachypnea of the newborn (TTN). It is brought on by a lag in the fetal alveolar fluid's postpartum clearance. **Objective**: To study the effect of early epinephrine inhalation versus salbutamol inhalation on the outcome of transient tachypnea of newborn and hospital course of admitted cases. **Patients and Methods:** A prospective randomized control study conducted at NICU during the period from December 2021 to May 2022. Study population: The current study involved include 150 neonates subdivided into three groups: Group A: 50 cases, infants in this group treated with conventional nasal canula, iv fluids, antibiotics and Ryle feeding. Group B: 50 cases, infants in this group treated as group A in addition to two doses of inhaled salbutamol 12 hours apart. Group C: 50 cases, infants in this group treated as group A in addition to two doses of inhaled epinephrine 12 hours apart. **Results**: salbutamol group showed significant lower respiratory rate after treatment compared to control group and adrenaline group ($p= 0.002$ & 0.005 respectively). There was significant increase in PaO2 after treatment compared to before treatment in control group ($p<0.001$), adrenaline group ($p<0.001$) and salbutamol group ($p<0.001$), while there was significant decrease in PaCO2 after treatment compared to before treatment in control group ($p<0.001$), adrenaline group ($p<0.001$) and salbutamol group ($p<0.001$). it was observed that salbutamol group had significant lower hospital stay duration compared to control group ($p=0.004$) **Conclusions**: Inhaled salbutamol resulted in better outcome than epinephrine inhalation in decreasing the TTN clinical score, lowering the FiO2, increasing the O2 saturation and decreasing the duration of respiratory support along with the total duration of hospitalization.

Key words: Transient tachypnea of the newborn, cesarean section, neonatal intensive care unit

Introduction

One of the most frequent causes of respiratory distress in newborns, particularly in late-preterm and term infants, is transient tachypnea of the newborn (TTN) [1]. TTN is brought on by a lag in the fetal alveolar fluid's postpartum clearance. Symptoms often disappear within 24-72 hours of age under supportive care management [2].

TTN affects less than 1% of all term infants and 10% of infants born between 33 and 34 weeks of gestation. It also affects 5% of infants delivered at 35 to 36 weeks [3].

In vivo studies have shown that the lung epithelium secretes Cl- and fluid throughout gestation but only later in the process does it begin to actively reabsorb Na+. In response to circulating catecholamines, the mature lung shifts at birth from active Cl- (fluid) secretion to active Na+ (fluid) absorption; evidence suggests glucocorticoids play a role in this switch. Changes in oxygen tension improve the epithelium's ability to transport Na+ and boost the expression of the epithelial Na+ channel (ENaC). The immature expression of ENaC, which can be up-regulated by glucocorticoids, prevents the immature fetal lung from transitioning from fluid production to fluid absorption. In late gestational age, glucocorticoids cause lung Na+ reabsorption most likely via the fetal lung alveolar ENaC channel [4].

The rationale behind utilizing salbutamol for a newborn's transient tachypnea is based on research demonstrating that β-agonist medications, including epinephrine (commonly known as adrenaline), might hasten the rate of fluid clearance from the lungs' tiny cavities (alveoli). evaluated for the first time the effectiveness of inhaled salbutamol on TTN [5].

When compared to the placebo group, they exhibited a significant reduction in the duration of hospital stays for newborns. It was also shown that salbutamol inhalation considerably shortened the duration of oxygen therapy.

However, it had no discernible impact on how long the tachypnea lasted. The forementioned investigations found no evidence of salbutamol's potential adverse effects, including tachycardia, arrhythmia, hypokalemia, and hyperglycemia [6].

Whether there was labor before the caesarean delivery or not , there is a higher risk of transiant tachypnea in the newborn for women who have undergone , laboring before having a caesarean section does not protect against the newborn's transient tachypnea [7].

Due to the immaturity of the ENaC transition, the absence of lamellar bodies for the synthesis of surfactant, and the general immaturity of the lung epithelium, late preterm newborns are more likely than full-term infants to experience transitory tachypnea of the newborn. For infants born beyond 35 weeks of pregnancy and whose mothers did not get prenatal steroids, the risk of poor respiratory outcomes is very significant [8].

Late preterm, term, and post-term neonates who have tachypnea (respiratory rate >60) and at least one radiological sign of transient tachypnea (such as lung hyperinflation, peripheral congestion or streaking, fluid-filled interlobar fissure, fluffy bilateral infiltration, and pulmonary edema) or symptoms of transient tachypnea with normal chest radiography [9].

But in certain newborns who exhibit brief tachypnea symptoms, pulmonary hypertension is followed by hypoxia, and the newborn may even require mechanical ventilation and extracorporeal membrane oxygenation in addition to suffering from major respiratory issues that could result in death [10].

Aim of the study

To study the effect of early epinephrine inhalation versus salbutamol inhalation in outcome of transient tachypnea of newborn and hospital course of admitted cases.

Patients and Methods

Study design: A randomized clinical trial conducted at NICU, Sohag teaching hospital during the period from first of December 2021 to May 2022.

Study population: The current study involved include 150 neonates subdivided into three groups: Group A: 50 cases, infants in this group treated with conventional nasal canula, iv fluids, antibiotics and Ryle feeding. Group B: 50 cases, infants in this group treated as group A in addition to two doses of inhaled salbutamol 12 hours apart. Group C: 50 cases, infants in this group treated as group A in addition to two doses of inhaled epinephrine 12 hours apart.

Inclusion criteria: Gestational age at birth 34 and 42 weeks of gestation. Diagnosis during the first 24 hours of life of transient tachypnea of the newborn, according to clinical and radiological findings.

Exclusion criteria: Gestational age at birth less than 34 weeks or greater than 42 weeks at birth. Infant with major cardiac disease. Infant with respiratory problem other than TTN. Infant with any congenital anomaly affecting respiratory status. non-respiratory causes of respiratory distress (polycythemia, hypoglycemia, neonatal sepsis, ……etc).

All participants had been subjected to the following: Complete medical history: Complete general examination. Complete chest examination. Transcutaneous oxygen measurement (pulse oximetry). Fraction of inspired oxygen (Fio2). Laboratory Investigations: Arterial blood gases. Complete blood count. C Reactive protein level. Erythrocyte Sedimentation Rate. Blood urea level. Serum Creatinine level. Serum glutamic-oxaloacetic transaminase level. Serum glutamic-pyruvic transaminase level. Random blood sugar level. Serum calcium level and chest X ray.

Ethics Approval

An approval of the study is obtained from Sohag teaching hospital and ethical committee, written consent had been obtained from parents of all cases prior to treatment plan and benefits from

participation in the research explained to parents of cases.

Statistical analysis:

Data was collected, coded then entered as a spread sheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data was analyzed using IBM Statistical Package for Social Sciences software (SPSS), (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median & IQR while categorical data as numbers and percentage. A statistical value <0.05 was considered as significant.

Results

There was no statistically significant difference between the three studied groups regarding gender and postnatal age (p>0.05). On the other hand, there was statistically significant difference between the three studied groups regarding weight (p= 0.013) as weight in salbutamol was significantly lower compared to control group (Table 1).

In table (2) there was statistically significant difference between the three studied groups regarding maternal history during pregnancy (p= 0.046). On the other hand, there was no statistically significant difference between the three studied groups regarding type of delivery and gestational age (p>0.05).

No gross congenital anomalies were observed in the three studied groups. Normal cardiac and abdominal examination was reported in the three studied groups. There was no statistically significant difference between the three studied groups regarding cyanosis (p>0.05) This table shows: The mean TTN score in control group was 2.38± 1.19, 2.36± 1.06 in adrenaline group and 2.34± 1.06 in salbutamol group. There was no statistically significant difference between the three studied groups regarding TTN score (p>0.05) (Table 4).

In table (5): There was no statistically significant difference between the three groups regarding oxygen saturation (p>0.05). Regarding respiratory rate, there was significant decrease in respiratory rate after treatment compared to before treatment in control group (p<0.001), adrenaline group (p<0.001) and salbutamol group (p<0.001). on the other hand, salbutamol group showed significant lower respiratory rate after treatment compared to control group and adrenaline group (p= 0.002 & 0.005 respectively). There was significant decrease in heart rate after treatment compared to before treatment in control group (p=0.023). On the other hand, adrenaline group and salbutamol group showed significant lower heart rate compared to control group before treatment (p= 0.001 & 0.015 respectively) and after treatment (p= 0.001 & 0.014 respectively).

There was no statistically significant difference between the three groups regarding PaO2 before and after treatment (p>0.05). There was significant increase in PaO2 after treatment compared to before treatment in control group (p<0.001), adrenaline group (p<0.001) and salbutamol group (p<0.001). Regarding PaCO2, there was no statistically significant difference between the three groups before and after treatment (p>0.05) while there was significant decrease in PaCO2 after treatment compared to before treatment in control group (p<0.001), adrenaline group (p<0.001) and salbutamol group (p<0.001). As regards pH, there was significant increase in pH after treatment compared to before treatment in control group (p<0.001), adrenaline group (p<0.001) and salbutamol group (p<0.001). Salbutamol group showed significant higher PH level before treatment compared to control group (p= 0.042) (Table 6).

There was no statistically significant difference between the three groups regarding hemoglobin, platelets count and WBCs (p>0.05). There was no

statistically significant difference between the three groups regarding blood urea, s. creatinine, SGOT and SGPT (p>0.05). Also, there was no statistically significant difference between the three groups regarding random blood sugar and s. calcium (p>0.05) (Table 7).

There was no statistically significant difference between the three studied groups regarding chest x-ray findings (p>0.05) (Table 8).

There was no statistically significant difference between the three studied groups regarding oxygen needed (p>0.05). On the other hand, oxygen need duration showed significant decline in salbutamol group compared to control group (p<0.001) and adrenaline group (p=0.042). Need for mechanical ventilation did not significantly differ among the three groups. There was statistically significant difference between the three studied groups regarding hospital stay (p=0.005) as it was observed that salbutamol group had significant lower hospital stay duration compared to control group (p=0.004) (Table 9).

Table (1): Demographic characteristics among the studied groups.

Item		Group (A) Control group (n.= 50)		Group (B) Adrenaline group (n.= 50)		Group (C) Salbutamol group (n.= 50)		Test value	P-value
		No.	%	No.	%	No.	%		
Gender	**Male**	28	56.0%	25	50.0%	28	56.0%	X^2= 1.867	0.393
	Female	22	44.0%	25	50.0%	22	44.0%		
Post-natal age (hours)	**Mean± SD**	2.52± 2.06		3.37± 2.08		2.92± 2.27		KW= 5.556	0.062
	Range	10 min. - 8 hours		30 min. - 8 hours		15 min. - 8 hours			
	Median	2.0		3.0		2.0			
Weight (grams)	**Mean± SD**	2615.0± 562.3		2351.0± 506.5		2296.0± 477.7		KW= 8.683	**0.013** P_{A-B}=0.068 P_{A-C}=**0.017** P_{B-C}= 1.00
	Range	1700-3800		1600-3500		1500-3500			
	Median	2725		2200		2200			

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test& KW: Kruskal-Wallis Test.

Table (2): Comparison between the studied groups regarding maternal & obstetric history.

Item		Group (A) Control group (n.= 50)		Group (B) Adrenaline group (n.= 50)		Group (C) Salbutamol group (n.= 50)		Test value	P-value
		No.	%	No.	%	No.	%		
Maternal history during pregnancy	No	42	84.0%	45	90.0%	48	96.0%	X^2= 9.67	**0.046**
	DM	4	8.0%	0	0.0%	0	0.0%		
	HTN	4	8.0%	5	10.0%	2	4.0%		
Type of delivery	CS	30	60.0%	29	58.0%	29	58.0%	X^2= 0.055	0.973
	NVD	20	40.0%	21	42.0%	21	42.0%		
Gestational age (weeks)	Mean± SD	37.68± 2.08		37.78± 2.14		37.32± 1.86		KW= 0.874	0.646
	Range	34- 42		34- 42		34- 41			
	Median	37.5		38		38			

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test& KW: Kruskal-Wallis Test.

Table (3): Comparison between the studied groups regarding TTN score.

Item		Group (A) Control group (n.= 50)	Group (B) Adrenaline group (n.= 50)	Group (C) Salbutamol group (n.= 50)	Test value	P-value
TTN score	Mean± SD	2.38± 1.19	2.36± 1.06	2.34± 1.06	KW= 0.010	0.995
	Range	1- 5	1- 4	1- 4		
	Median	2	2	2		

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test& KW: Kruskal-Wallis Test.

Table (4): Comparison between the studied groups regarding examination.

Item		Group (A) Control group (n.= 50)		Group (B) Adrenaline group (n.= 50)		Group (C) Salbutamol group (n.= 50)		Test value	P-value
		No.	%	No.	%	No.	%		
Gross congenital anomalies	No	50	100.0%	50	100.0%	50	100.0%	NA	NA
	Yes	0	0.0%	0	0.0%	0	0.0%		
Cyanosis	Non	38	76.0%	38	76.0%	38	76.0%	X^2= 0.262	0.992
	At extremities	8	16.0%	8	16.0%	9	18.0%		
	Central	4	8.0%	4	8.0%	3	6.0%		
Cardiac examination	Normal	50	100.0%	50	100.0%	50	100.0%	NA	NA
	Abnormal	0	0.0%	0	0.0%	0	0.0%		
Abdominal examination	Normal	50	100.0%	50	100.0%	50	100.0%	NA	NA
	Abnormal	0	0.0%	0	0.0%	0	0.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test& KW: Kruskal-Wallis Test.

Table (5): Comparison between the studied groups regarding vital signs.

Item	Group (A) Control group (n.= 50)					Group (B) Adrenaline group (n.= 50)					Group (C) Salbutamol group (n.= 50)					Test value	P-value
	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.		
	Oxygen saturation																
	92.12	3.46	92.00	84.00	98.00	93.10	4.61	94.00	82.00	99.00	93.12	4.26	94.00	81.00	99.00	3.98	0.137
Respiratory rate																	
Before	73.98	4.65	74.00	65.00	85.00	72.78	4.58	73.00	65.00	83.00	73.44	4.94	73.00	65.00	85.00	1.606	0.448
After	60.76	5.03	61.50	47.00	70.00	60.60	5.69	60.00	48.00	75.00	57.14	7.11	56.00	43.00	80.00	14.35	**0.001** P_{A-B}=1.00 P_{A-C}=**0.002** P_{B-C}=**0.005**
Test value	6.166					6.168					6.159						
p-value	**<0.001**					**<0.001**					**<0.001**						
	Heart rate																
Before	148.98	10.33	147.50	127.00	170.00	141.48	10.06	140.00	125.00	167.00	142.50	10.03	143.50	125.00	165.00	13.90	**0.001** P_{A-B}=**0.001** P_{A-C}=**0.015** P_{B-C}=1.00
After	146.10	5.94	145.00	130.00	160.00	141.22	7.32	141.50	125.00	160.00	142.66	8.12	142.00	130.00	163.00	14.26	**0.001** P_{A-B}=**0.001** P_{A-C}=**0.014** P_{B-C}=1.00
Test value	2.272					0.068					0.126						
p-value	**0.023**					0.946					0.900						

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, Comparison between group done by Independent-Samples Kruskal-Wallis Test & inside the same group indifferent period by Wilcoxon signed rank test

Table (6): Comparison between the studied groups regarding ABG before and after treatment.

Item	Group (A) Control group (n.= 50)					Group (B) Adrenaline group (n.= 50)					Group (C) Salbutamol group (n.= 50)					Test value	P-value
	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.		
PaO2																	
Before	70.36	13.42	72.00	40.00	92.00	73.44	17.75	79.00	30.00	96.00	73.52	16.27	78.50	30.00	96.00	3.01	0.222
After	81.14	9.93	83.00	63.00	97.00	80.12	13.07	84.00	47.00	96.00	81.70	12.06	85.00	55.00	100.00	0.38	0.826
Test value	6.158					5.850					6.162						
p- value	**<0.001**					**<0.001**					**<0.001**						
PaCO2																	
Before	41.08	4.40	40.00	33.00	50.00	39.48	2.60	39.00	35.00	47.00	39.58	2.92	39.50	32.00	47.00	4.03	0.133
After	38.50	2.15	38.00	35.00	44.00	37.68	2.27	37.00	32.00	45.00	36.84	3.59	37.50	25.00	42.00	5.39	0.068
Test value	4.134					4.092					4.590						
p- value	**<0.001**					**<0.001**					**<0.001**						
pH																	
Before	7.36	.03	7.35	7.28	7.41	7.37	.02	7.37	7.32	7.40	7.37	.02	7.37	7.30	7.42	7.47	**0.024** P_{A-B}=0.07 P_{A-C}=**0.042** P_{B-C}=1.00
After	7.38	.02	7.37	7.35	7.42	7.38	.02	7.38	7.33	7.41	7.38	.02	7.38	7.27	7.41	1.998	0.368
Test value	3.872					2.618					2.581						
p- value	**<0.001**					**<0.001**					**0.01**						

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, Comparison between group done by Independent-Samples Kruskal-Wallis Test &inside the same group before and after treatment by Wilcoxon signed rank test

Table (7): Comparison between the studied groups regarding laboratory findings.

Item	Group (A) Control group (n.= 50)					Group (B) Adrenaline group (n.= 50)					Group (C) Salbutamol group (n.= 50)					Test value	P-value
	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.	Mean	± SD	Median	Min.	Max.		
Hemoglobin (g/dl)	16.53	.91	16.50	15.00	18.00	16.59	.99	16.55	15.00	18.00	16.41	.96	16.30	15.00	18.00	0.887	0.642
WBCs (×103/L)	14304	3044	14500	8000	20000	15350	2933	15900	9000	20000	15680	2844	15900	10000	20000	4.977	0.083
PLT(×103/L)	325.80	63.47	325.00	230.00	450.00	337.80	67.79	330.00	240.00	450.00	346.20	63.64	345.00	230.00	460.00	2.368	0.306
ESR	8.64	2.82	8.00	4.00	16.00	8.24	3.40	8.00	3.00	17.00	7.40	2.93	7.00	3.00	14.00	3.704	0.157
Blood urea (mmol/L)	8.05	2.83	8.15	3.20	13.00	7.90	2.95	8.40	3.00	13.00	7.51	2.84	7.50	3.00	13.00	1.044	0.593
S. creatinine (mg/dl)	0.50	0.22	0.50	0.20	0.90	0.57	.24	0.60	0.20	0.90	0.54	0.24	0.55	0.20	0.90	2.039	0.361
SGOT (U/L)	20.26	6.34	19.00	10.00	32.00	20.62	5.87	21.00	10.00	30.00	21.84	5.46	22.00	11.00	31.00	1.935	0.380
SGPT(U/L)	23.62	8.17	22.00	10.00	39.00	26.06	8.09	25.50	11.00	39.00	26.20	8.91	29.00	10.00	39.00	2.937	0.230
RBS (mg/dl)	75.74	15.52	74.00	46.00	110.00	78.30	12.35	77.50	56.00	100.00	77.98	12.25	77.50	57.00	100.00	1.103	0.576
S. Ca (mg/dl)	9.43	.60	9.45	8.50	10.50	9.44	.60	9.50	8.50	10.50	9.50	.58	9.50	8.50	10.50	0.398	0.820

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, Comparison between group done by Independent-Samples Kruskal-Wallis Test

Table (8): Comparison between the studied groups regarding chest x-ray.

Item		Group (A) Control group (n.= 50)		Group (B) Adrenaline group (n.= 50)		Group (C) Salbutamol group (n.= 50)		Test value	P-value
		No.	%	No.	%	No.	%		
Chest x-ray	Normal	33	66.0%	35	70.0%	36	72.0%	X^2= 1.579	0.813
	Mild interstitial pulmonary edema	3	6.0%	5	10.0%	4	8.0%		
	Streaks of fluid	14	28.0%	10	20.0%	10	20.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test

Table (9): Comparison between the studied groups regarding outcome.

Item		Group (A) Control group (n.= 50)		Group (B) Adrenaline group (n.= 50)		Group (C) Salbutamol group (n.= 50)		Test value	P-value
		No.	%	No.	%	No.	%		
Oxygen needed	Conventional nasal oxygen	36	72.0%	39	78.0%	36	72.0%	X^2= 0.624	0.732
	CPAP	14	28.0%	11	22.0%	14	28.0%		
Oxygen need duration (hours)	Mean± SD	42.6± 13.73		37.12± 21.79		30.88± 20.30		KW= 17.74	**<0.001** P_{A-B}=0.250 P_{A-C}=**<0.001** P_{B-C}=**0.042**
	Range	12- 72		12- 108		6- 96			
	Median	48		36		24			
Need for mechanical ventilation	No	50	100.0%	48	96.0%	47	94.0%	X^2= 2.897	0.235
	Y#es	0	0.0%	2	4.0%	3	6.0%		
Hospital stay (hours)	Mean± SD	68.26± 20.32		64.08± 27.71		55.20± 28.38		KW= 10.48	**0.005** P_{A-B}=0.403 P_{A-C}=**0.004** P_{B-C}=0.246
	Range	36- 120		24- 144		24- 144			
	Median	36		60		48			

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X^2: Chi-Square Test& KW: Kruskal-Wallis Test.

Discussion

Among term newborns, postnatal respiratory problems are frequent. Transient tachypnea of the newborn is the most frequently mentioned cause of neonatal respiratory distress in late preterm infants. According to reports, the condition is benign and self-limiting, and resolution often happens between 2 and 5 days after birth. There have been reports of consequences such pneumothorax, the necessity for extracorporeal membrane oxygenation, and mortality in rare severe cases of newborns with transient tachypnea [11]. The development of the fetal lung to fully transition from intrauterine to extrauterine life depends on the existence of a suitable volume of lung fluid throughout gestation. While some interstitial lung liquid drains through0 the lung lymphatic channels, the majority travels into the pulmonary circulation [12]. Transient tachypnea of the newborn is believed to result from delayed resorption of fluid from the lungs of the newborn, which is an important diagnostic and therapeutic dilemma in the NICU [13]. TTN development may be significantly influenced by the fetal lung's inability to switch from fluid secretion to fluid absorption and an immaturity in the expression of the ENaC. It is possible to utilize inhaled or intravenous beta adrenergic agonists to treat pulmonary edema and acute lung injury, according to both experimental and limited clinical evidence in adult patients that show significant extra fluid clearance from the alveolar airspace. In the treatment of a newborn's transient tachypnea, aerosolized beta agonists have been utilized to minimize the systemic side effects of beta agonists [14].

The aim of this study was to study the effect of early epinephrine inhalation versus salbutamol inhalation in outcome of transient tachypnea of newborn and hospital course of admitted cases. Demographic characteristics among the studied groups. There was no statistically significant difference between the three studied groups regarding gender and

postnatal age (p>0.05),but there was predominance for males than females(54%:46%) which was in agreement with Nawar et al. [15] study as there was predominance for males than females (58.3%: 41.6%) and Armangil et al. [5]; Kao et al. [16] who observed male predominance in TTN. Moresco et al. [17] evaluated the efficacy of salbutamol administration in the treatment of transient tachypnea of the newborn in infants born at 34 weeks' gestational age or more. Seven trials, including 498 infants, met the inclusion criteria of this updated review. The mean gestational age in the included studies was 37 weeks. Very low-certainty evidence suggests that salbutamol may reduce duration of oxygen therapy (which was shorter in the salbutamol group by 19 hours) and duration of respiratory support; there was no difference in the need for continuous positive airway pressure and need for mechanical ventilation. Low certainty evidence suggests that salbutamol may reduce duration of hospital stay. Five trials are ongoing. In our study there was statistically significant difference between the three studied groups regarding maternal history during pregnancy (p= 0.046) as 4 neonates had maternal history of gestational DM and 11 neonate had maternal history of HTN. On the other hand, there was no statistically significant difference between the three studied groups regarding type of delivery and gestational age but there was predominance for CS delivery than NVD (58.7%:41.3%).

In a similar work of Nawar et al [(15)] the aim of this study was to study the effect of early epinephrine inhalation versus salbutamol inhalation in outcome of transient tachypnea of newborn and hospital course of admitted cases. Demographic characteristics among the studied groups. There was no statistically significant difference between the three studied groups regarding gender and postnatal age (p>0.05), but there was predominance for males than females(54%:46%) which was in

agreement with Nawar et al. [15] study as there was predominance for males than females (58.3%: 41.6%) and Armangil et al. [5]; Kao et al. [16] who observed male predominance in TTN. Moresco et al. [17] evaluated the efficacy of salbutamol administration in the treatment of transient tachypnea of the newborn in infants born at 34 weeks' gestational age or more. Seven trials, including 498 infants, met the inclusion criteria of this updated review. The mean gestational age in the included studies was 37 weeks. Very low-certainty evidence suggests that salbutamol may reduce duration of oxygen therapy (which was shorter in the salbutamol group by 19 hours) and duration of respiratory support; there was no difference in the need for continuous positive airway pressure and need for mechanical ventilation. Low certainty evidence suggests that salbutamol may reduce duration of hospital stay. Five trials are ongoing. In our study there was statistically significant difference between the three studied groups regarding maternal history during pregnancy (p= 0.046) as 4 neonates had maternal history of gestational DM and 11 neonate had maternal history of HTN. On the other hand, there was no statistically significant difference between the three studied groups regarding type of delivery and gestational age but there was predominance for CS delivery than NVD (58.7%:41.3%). Nawar et al. [15] study, caesarian section was the mode of delivery of 37 neonates (61.6%) , eight neonates (13%) had history of maternal gestational diabetes while 6 (10%) had history of maternal asthma, and this was in agreement with Davies et al. [18] who found that main risk factors for TTN are cesarean delivery, large birth weight, maternal gestational diabetes, maternal asthma, twin pregnancy, and male gender, also Hamed et al. [19] found that the most common risk factors in studied cases according to maternal history: were born by CS in 82% in salbutamol group and 88% in non- salbutamol group followed by premature delivery in 42% and 48%

respectively, SGA in 40% and 38% respectively but there was insignificant differences between two groups as regard maternal risk factors. According to Hansen et al. [20] data from 34,458 newborns in Denmark at a single university hospital, which showed that infants delivered by ECS at 37 weeks had a 10% incidence of respiratory morbidity (defined as TTN, RDS or pulmonary hypertension of the newborn [PPHN]) compared with 2.8% among infants delivered vaginally (OR: 3.7; 95% CI: 2.2–6.1). At 40 weeks, the rate of respiratory morbidity with ECS decreased to 1.5% and there was no significantly different from the respiratory rate seen in babies with vaginal deliveries. The mean TTN score in control group was 2.38± 1.19, 2.36± 1.06 in adrenaline group and 2.34± 1.06 in salbutamol group. There was no statistically significant difference between the three studied groups regarding TTN score, in disagreement with our results, Bakry et al. [21] showed that there is significant difference in TTN score between groups before initiation of study. Accidentally, salbutamol group cases were worse more than control group cases in TTN score before initiation of study in spite of randomization.

In disagreement with our results, Al Lahony et al. [22] found that there was statistically significant difference between the three studied groups regarding TTN score. There was no statistically significant difference between the three groups regarding oxygen saturation. Regarding respiratory rate, there was significant decrease in respiratory rate after treatment compared to before treatment in control group, adrenaline group and salbutamol group on the other hand, salbutamol group showed significant lower respiratory rate after treatment compared to control group and adrenaline group. Concerning heart rate, there was no significant rise in heart rate after treatment compared to before treatment in control group (p=0.023). On the other hand, adrenaline group and salbutamol group showed significant

lower heart rate compared to control group before treatment (p= 0.001 & 0.015 respectively) and after treatment In agreement with our results Nawar et al. [15] showed that there was significant difference between groups in heart rate before and after nebulization but adrenaline group recorded the highest readings in comparison to the other groups after nebulization. There was significant difference between groups in respiratory rate after 1 & 4 hours, salbutamol group recorded the least readings in comparison to the other groups. In salbutamol group: there was no significant change in heart rate but significant decrease in respiratory rate 4 hours after nebulization in comparison to base line readings. No significant difference was recorded for HR in the difference between after 4h and before. However, a significant difference was recorded in RR group II for the difference between after 4h and before, similarly Bakry et al. [21] showed that four hours after management there was significant decrease ($P < 0.001$) in respiratory rate which is 64.80 (± 4.14) in salbutamol group versus 74.12 (±5.85) in control group, also there was significant decrease ($P < 0.001$) in TTN score which is 5.08±1.58 in salbutamol group versus 7.32±0.85 in control group 4 hours after enrollment in study. Also in agreement with our results, in Yurdakok et al. [23] study they observed that the respiratory rate decreased with salbutamol inhalation than control and epinephrine group. Similar to Nawar et al. [15] results, Armangil et al. [5] found that inhaled salbutamol in infants with TTN, decreases in respiratory rate, and TTN clinical score significantly while non-significant difference regarding heart rate was detected; also they found the improvement in the level of respiratory support was statistically significant with inhaled salbutamol that was in agreement with Yurdakok et al. [23]. On the other hand Kao et al. [16], found no significant difference between inhaled epinephrine and saline inhalation regarding clinical

data. There was no statistically significant difference between the three groups regarding hemoglobin, platelets count and WBCs (p>0.05). There was no statistically significant difference between the three groups regarding blood urea, s. creatinine, SGOT and SGPT (p>0.05). Also, there was no statistically significant difference between the three groups regarding random blood sugar and s. calcium. There was significant increase in PaO2 after treatment compared to before treatment in control group, adrenaline group and salbutamol group. Regarding PaCO2, there was no statistically significant difference between the three groups before and after treatment (p>0.05) while there was significant decrease in PaCO2 after treatment compared to before treatment in control group, adrenaline group and salbutamol group. As regards pH, there was significant increase in pH after treatment compared to before treatment in control group, adrenaline group and salbutamol group. On the other hand, salbutamol group showed significant higher pH before treatment compared to control group. In agreement with our results Nawar et al. [15] showed that there were significant differences between groups in pH, PaO2, PaCO2after nebulization. Saline group recorded the lowest readings of pH and PaO2 in comparison to the other groups, but the highest reading in PaCO2. In salbutamol group: there was significant increase in PH, PaO2 and significant decrease in PaCO2 after nebulization. On the other hand, the difference between after and before exhibited a significant difference in group I and II for pH. There was significant difference between groups in O2 after 1 & 4 hours. Adrenaline group recorded the lowest readings in comparison to the other groups. There was significant difference between groups in FiO2 after 4 hours, salbutamol group recorded the least readings in comparison to the other groups. For SpO2, difference between after and before recorded a significant difference in group II. Also,

the same result for FiO2 was recorded. Nawar et al. [15] showed that regarding ABG findings after intervention, PH, PaO2 and O2 saturation were significantly higher in group II (inhaled salbutamol), PaCO2, FiO2 were significantly lower in group II. Similar to Nawar et al. results Armangil et al. [5], found significantly higher PH, PaO2 and significantly lower PaCO2, FiO2 in salbutamol group, also Al Lahony et al. [22] showed that there is a highly significant improvement in salbutamol group regarding arterial blood gas findings (pH, PaO2, and PaCO2) after 4 h of therapy rather than saline group, in the form of higher pH and PaO2 after 4 hours and lower PaCO2 after 4 hours.

Mohammadzadeh et al. [24] showed that the mean values of respiratory rate, heart rate, FiO2, retraction score, oxygen saturation, enteral feeding initiation, duration of oxygen therapy and hospitalization was not different between groups. But based on paired t-test analysis the mean values of the respiratory rate, FiO2 and retraction score in before and 24 hours after the initiation of the study was significantly decreased in both groups. There was no statistically significant difference between the three studied groups regarding oxygen needed ($p>0.05$). On the other hand, oxygen need duration showed significant decline in salbutamol group compared to control group, and adrenaline group ($p=0.042$). Need for mechanical ventilation did not significantly differ among the three groups. There was statistically significant difference between the three studied groups regarding hospital stay ($p=0.005$) as it was observed that salbutamol group had significant lower hospital stay duration compared to control group ($p=0.004$). In agreement Armangil et al. [5] reported that median duration of hospital stay was 4 days (interquartile range 2 to 5) in the salbutamol group versus 6 days (interquartile range 4 to 7) in the placebo group ($P = 0.002$), also Hamed et al. [19] found that there was significant improvement in both groups with higher improvement in Salbutamol

group. 92% of cases received salbutamol needs oxygen therapy and 8% needs CPAP in comparison to other group with no salbutamol 60% needs oxygen therapy and 40% needs CPAP. There was significant decreased in hospital stay among cases received salbutamol versus no salbutamol. Similarly, Bakry et al. [21] showed that there is significant decrease in total duration of oxygen therapy, hospitalization and time before initiating enteral feeding in hours in salbutamol group.

Conclusions

This prospective trial showed that two doses of inhaled salbutamol resulted in better outcome than epinephrine inhalation in decreasing the respiratory rate, decreasing the TTN clinical score, lowering the FiO2, increasing the O2 saturation and decreasing the duration of respiratory support along with the total duration of hospitalization.

Acknowledgements

The study group is grateful to the NICU team, Sohag teaching hospital for their support.

Author's contributions

The study conception and design were done by DA and HA. Laboratory investigations were performed and analyzed by AH. Data acquisition by AY and AH. Analysis and interpretation were performed by all members of the group. The authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Funding

The manuscript was funded by the authors

Author's details

[1]Department of pediatrics, Ministry of health, Sohag Government, Egypt

[2]Department of pediatrics, faculty of Medicine, Al-Azhar university (Assuit), Egypt

[4]Department of clinical-pathology, faculty of Medicine, Al-Azhar university (Assiut), Egypt

Date received: 7th September 2023, accepted 9th November 2023

References

1- Kumar, A., & Vishnu Bhat, B.: Epidemiology of respiratory distress of newborns. The Indian Journal of Pediatrics,1996; 63(1): 93-98.

2- Hagen E, Chu A, Lew C. (2017): Transient tachypnea of the newborn. New reviews;18:e141-e148 .

3- Raju, T. N., Higgins, R. D., Stark, A. R., & Leveno, K. J.: Optimizing care and outcome for late-preterm

(near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006, 118(3): 1207-1214.

4- Hooper, S. B., Polglase, G. R., & Roehr, C. C. J. P. r. r. : Cardiopulmonary changes with aeration of the newborn lung 2015, 16(3): 147-150 .

5- Armangil, D., Yurdakök, M., Korkmaz, A., Yiğit, Ş., & Tekinalp, G.: Inhaled beta-2 agonist salbutamol for the treatment of transient tachypnea of the newborn. The Journal of pediatrics 2011, 159(3): 398-403.

6- Malakian, A., Dehdashtian, M., Aramesh, M. R., Aletayeb, M. H., & Heidari, S.: The effect of inhaled salbutamol on the outcomes of transient tachypnea of the newborn. Journal of the Chinese Medical Association 2018, 81(11): 990-997.

7- Silasi, M., Coonrod, D. V., Kim, M., & Drachman, D.: Transient tachypnea of the newborn: is labor prior to cesarean delivery protective. American journal of perinatology 2010, 27(10): 797-802.

8- Riskin, A., Abend-Weinger, M., Riskin-Mashiah, S., Kugelman, A., & Bader, D.: Cesarean section, gestational age, and transient tachypnea of the newborn: timing is the key. American journal of perinatology 2005, 22(07): 377-382.

9- Akbarian, M., Veshkini, A., Masoudifard, M., & Mortazavi, P.: Comparative evaluation of interstitial lung pattern by analog radiography and computed radiography in domestic shorthair cats. Journal of Comparative Pathobiology 2018, 15(2): 2479-2486.

10- Gupta, S., & Li, L.: Modulation of miRNAs in pulmonary hypertension. International journal of hypertension, 2015:41-59

11- Gulersen, M., Gyamfi-Bannerman, C., Greenman, M., Lenchner, E., Rochelson, B., & Bornstein, E.: Time interval from late preterm antenatal corticosteroid administration to delivery and the impact on neonatal outcomes. American Journal of Obstetrics & Gynecology MFM 2021, 3(5): 100426.

12- Alhassen, Z., Vali, P., Guglani, L., Lakshminrusimha, S., & Ryan, R. M. J. J. o. P.: Recent advances in pathophysiology and management of transient tachypnea of newborn. 2021, 41(1): 6-16 .

13- Ammirabile, A., Buonsenso, D., & Di Mauro, A.: Lung ultrasound in pediatrics and neonatology: an update. In Healthcare 2021, 9(8):1015: MDPI.

14- Laube, M., & Thome, U. H.: Y It Matters—Sex Differences in Fetal Lung Development. Biomolecules, 2022, 12(3): 437.

15- Nawar, F., Aly, H. A., Helmy, S., & Monaem, M. A. E.: Is Salbutamol and Adrenalin Inhalation Effective in Management of Transient Tachypnia of Newborn?. Br J Med Med Res 2016; 8:30-48

16- Kao, B., Stewart de Ramirez, S. A., Belfort, M. B., & Hansen, A.: Inhaled epinephrine for the treatment of transient tachypnea of the newborn. Journal of Perinatology, 2008; 28(3): 205-210.

17- Moresco, L., Bruschettini, M., Macchi, M., & Calevo, M. G. (2021): Salbutamol for transient tachypnea of the newborn. Cochrane Database of Systematic Reviews 2021, (2):87-98

18- Davies, J. C.: Ion transport in lung disease. Pediatric pulmonology. Supplement, 2004; 26, 147-148.

19- Hamed, A. M., El-Lebedy, I. M., & Hamza, K. A.: The Rule of Inhaled Salbutamol on The Outcome of Transient Tachypnea of Newborn. Annals of Neonatology Journal, 2022; 4(2): 98-112.

20- Hansen, A. K., Wisborg, K., Uldbjerg, N., & Henriksen, T. B.: Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. Bmj, 2018; 336(7635): 85-87.

21- Bakry, A. R., Atia, A. A. E. L., Hablas, H. R., & Abd El Aziz, A. F.: The role of inhaled β2-adrenergic agonists in treatment of transient tachypnea of the newborn. Al-Azhar Journal of Pediatrics, 2019; 22(1): 57-74.

22- Al Lahony, D. M., Elsayed, H. M., & Mohammed, I. S.: The effects of inhaled β-adrenergic agonists in transient tachypnea of the newborn. Menoufia Medical Journal 2020, 33(3): 847.

23- Yurdakok, M., & Ozek, E.: Transient tachypnea of the newborn: the treatment strategies. Current pharmaceutical design, 2012; 18(21): 3046-3049.

24- Mohammadzadeh, I., Akbarian-Rad, Z., Heidari, F., Zahedpasha, Y., & Haghshenas-Mojaveri, M. J. I. J. o. P.: The effect of inhaled salbutamol in transient of tachypnea of the newborn: a randomized clinical trial. 2017; 27(5):66-83

Citation: Ali, N., Ahmed, Y., Ahmed, H., Sayed, A. Inhaled Salbutamol Versus Epinephrine in Treatment of Transient Tachypnea of Newborn (TTN): A Randomized Control Trial. *Annals of Neonatology*, 2024; 6(1): 57-77. doi: 10.21608/anj.2023.239961.1076