RANDOMIZED CONTROLLED TRIAL OF RESTRICTIVE FLUID MANAGEMENT VERSUS BUDESONIDE INHALATION IN TRANSIENT TACHYPNEA OF THE NEWBORN INFANTS

By

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ABSTRACT

Background: *Transient tachypnea of the newborn (TTN) is considered as one of the most common respiratory disorders affecting 0.5% – 4% of all of the neonate full-term and post-term neonates, especially those who are delivered by cesarean section due to lack of the squeezing effect of the lungs by genital tract of mother. It is caused mainly due to lung edema, which is the result of delayed absorption of fluids of the lung alveoli in the fetus.*

Objective: *To study the effect of Restrictive Fluid Management versus Early Budesnide Inhalation in outcome of Transient Tachypnea of the Newborn infants and on the Hospital course of neonates with (TTN).*

Patients and Methods: *This comparative analytic study that was conducted at department of neonatology at Al-Azhar University Hospital and Sohag Teaching Hospital from 1st March 2021 to 1st January 2022 on 150 neonate aged between (34 to 37 weeks) subdivided into three groups:*

Group I (50 cases): *infants in this group treated by ordinary management of TTN in the form of ordinary intra venous fluid , respiratory support if needed in form of t: continuous positive end-expiratory pressure (CPAP), high flow nasal CPAP (HFNCPAP), or conventional nasal cannula (NC), intravenous fluid, antibiotics, rayl feeding.* ***Group II (50 cases):*** *infants in this group treated by restriction of fluid therapy 50- 65 mL/kg and 65- 80 mL /kg for term and preterm neonates, respectively in addition to ordinary management of TTN.* ***Group III (50 case):*** *Infants in this group were randomized to have two doses, 12 h apart, of inhaled Budesonide 1000µg/dose within 6 h from delivery, in addition to ordinary management of TTN support if needed.*

All studied groups subjected to complete history, clinical and laboratory examination.

Results: *In the current study we found that there was significant improvement between the 3 groups as regard FIO_2, Pao_2 and $paCO_2$ and Ph after treatment in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group. There was insignificant differences between three groups as regard pretreatment RR, HR but as regard post treatment score there was significant improvement in group received restricted fluid than other groups followed by ordinary treatment group then inhaled budesonide group. The duration of hospitalization was shorter in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group with significant differences. As regard need for MV or oxygen therapy there was insignificant differences between three groups.*

Conclusion: *The present study demonstrated that the restrictive fluid management can decrease the hospitalization period, respiratory support period, and the respiratory distress score in the neonates with transient tachypnea, and was better than ordinary treatment and steroid inhalation in the form of Budosonide inhalation. Fluid restriction appears safe in late preterm and term neonates with uncomplicated TTN. Early inhaled budesonide steroid was associated with improvement in respiratory functions, decreasing the signs of respiratory distress and significantly reducing the TTN clinical manifestations.*

Keywords: *Transient tachypnea of the newborn, Budesonide, Fluid restriction.*

INTRODUCTION

Transient tachypnea of the newborn (TTN) is a diagnosis given to infants born between 34 and 42 weeks gestation who develop difficulty breathing during the first days of life when no specific cause of the breathing difficulty can be identified. Little is known about why some babies develop TTN, and there have not been many formal studies of the best way to take care of babies with this disease. Babies with TTN get better on their own within three to five days after birth, but may require extra oxygen to breathe well **(Helve et al., 2007)**.

Most physicians believe that the symptoms of TTN are related to poor clearance of fluid from the newborn's lungs. Babies with TTN have extra fluid visible on chest x-ray. Diuretics, medicines that can help clear extra lung fluid in adults and in babies with extra lung fluid for other reasons, do not to help babies with TTN. Babies with TTN need intravenous fluids to be healthy because they breathe too fast to be able to start feeding. Breastfed babies only get a very small amount of fluid in the first few days of life, as it normally takes several days for a new mother to begin producing breastmilk. No one has yet examined whether giving babies with TTN an amount of fluid similar to the small amount they would receive if they could

breastfeed would help them recover from TTN faster **(Jain and Dudell, 2006)**.

Transient tachypnea of the newborn (TTN) is one of the most common causes of respiratory distress in the newborn period affecting 0.5% – 4% of all late preterm and term neonates. The symptoms of respiratory distress typically start within the first several hours after birth and result from failure of adequate absorption of fetal lung fluid. Studies have consistently shown that risk factors for TTN include prematurity, birth by cesarean delivery and male sex **(Parker and Kinsella, 2018)**.

TTN is one of the major causes for great number of the hospitalization of the late-preterm (34 to 36 weeks), term (37 to 42 weeks), and post-term (more than 42 weeks) neonates in the neonatal intensive care unit (NICU). TTN is usually a benign syndrome, started precisely after birth and is treated in 72-96 hours of life **(Martin et al., 2014)**.

In pathophysiology of this syndrome this delayed reabsorption of the fluid by the neonate's pulmonary system lead to effusion of the fluid in the neonate's lungs **(Dehdashtian et al., 2014)**.

The absence of mechanical forces that normally aid pulmonary fluid clearance, result of a delay in the absorption of the fluid by a neonate's lungs, may also contribute to TTN in neonates who undergo Cesarean section delivery **(Jain and Dudell, 2006)**.

The delayed reabsorption of lung fluids leads to impairment of gas exchange in the alveoli, as the fluid occupies the position of air, thereby decreasing the amount of air and minimizing the gas exchange which will lead to decrease the oxygen supply to the tissues and accumulation of CO2. Neonates with TTN may need noninvasive respiratory procedures (e.g., nasal cannula, nasal continuous positive airway pressure [CPAP] and require supplemental O_2 to sustain normal O_2 levels. Some cases may develop "malignant TTN," leading to serious persistent pulmonary hypertension of neonates; hence, the treatment of TTN has become important **(Ozalkaya et al., 2015)**.

Epithelial Na+channel (ENaC) is sensitive to the level of corticosteroids and is considered as one of the most important pathways through which absorption of lung fluids takes place. Corticosteroids had an important role in improving the functions of these specific Na+

channels in the lung by increasing the effectiveness of ENaC, leading to the functional maximization of these receptors in the absorption of lung fluids **(Jain and Dudell, 2006)**.

TTN of the late preterm, term, and post-term neonates with tachypnea (respiratory rate>60) with 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 **(Akbarian et al., 2018)**.

However, in some of the newborns that show the symptoms of transient tachypnea, pulmonary hypertension is followed by hypoxia and the neonate will even need mechanical ventilation and extracorporeal membrane oxygenation and undergo serious respiratory problem possibly leading to death **(Gupta et al., 2021)**.

Mild fluid restriction appears safe in late preterm and term neonates with uncomplicated TTN. Fluid restriction may be of benefit in decreasing duration of respiratory support and hospitalization charges in term and late preterm neonates with uncomplicated severe TTN **(Akbarian Rad et al., 2018)**.

The neonates with the gestational age ≥ 34 weeks suffering from TTN during the first 6 h after birth were randomized restrict the amounts of total fluid 50, 65 mL/kg and 65, 80 mL /kg for term and preterm neonates, respectively. In each group, a daily amount of 20 mL/kg fluid was added until 150 and 170 mL/kg for term and preterm newborns, in addition to ordinary treatment of TTN and oxygen therapy **(Akbarian Rad et al., 2018)**.

The inhaled corticosteroid intervention is preferred over systemic corticosteroids due to the possible side effects of the latter. Inhaled corticosteroid intervention has shown proven efficacy and safety in the treatment of many respiratory diseases, such as bronchial asthma, in infants as well as children. Local corticosteroid inhalation by the lungs decreases the prevalence of respiratory disorders and respiratory complications, such as bronchopulmonary dysplasia, pneumonia, and other disorders, without causing any systemic major adverse side effects in neonates **(Delara et al., 2019)**.

Infants born at >34 weeks gestational age with TTN at 4 h of

age were randomized to two doses, 12 h apart, of inhaled Budesonide 1000µg/dose within 6 h from delivery **(Vaisbourd et al., 2017)**.

AIM OF THE WORK

To study the effect of Restrictive Fluid Management versus Early Budesonide Inhalation in outcome of Transient Tachypnea of the Newborn Infants and on the Hospital course of these neonates.

PATIENTS AND METHODS

Type of study: comparative analytic analysis.

Sample size: as regard study and publication: 150 neonate aged between 34 to 37 weeks neonates subdivided statically by simple randomization into three groups:

Group I (50 cases): infants in this group treated by ordinary management of TTN for 3 days in the form of respiratory support: continuous positive end-expiratory pressure (CPAP), high flow nasal CPAP(HFNCPAP), or conventional nasal cannula (NC), intravenous fluid, antibiotics, ryle feeding.

Group II (50 cases): infants in this group treated for 3 days by restriction of fluid therapy (50- 65 mL/kg) and (65- 80 mL /kg) for term and preterm neonates≥34 wks, respectively. In each group, a daily amount of 20 mL/kg fluid was added until 150 and 170 mL/kg for term and preterm newborns, in addition to ordinary treatment of TTN and oxygen thereby), in addition to ordinary management of TTN.

Group III (50 case): Infants in this group were randomized to have two doses, 12 h apart, of inhaled Budesonide 1000µg/dose within 6 h from delivery, in addition to ordinary management of TTN for 3 days.

Study population: the included prospective study population was neonate with mild to moderate RDs, attended at department of neonatology at Al-Azhar University Hospital and Sohag Teaching Hospital.

Ethical considerations:

1. An approval of the study is obtained from Al-Azhar University Hospital and Sohag Teaching Hospital ethical committee.
2. The aim of study was explained to the parents of each participant before collection of data.
3. Oral and written consent were obtained from parents of all cases prior to treatment plan, and benefits from participation in the research explained to parents of cases.

4. All the data of the patients and results of the study are confidential & the patients have the right to keep it and Privacy of all dates was assured.
5. The author received no financial support for the research, authorship and/or publications of this article were needed.
6. No conflict of interest regarding the study or publication.

Inclusion criteria: All neonates presented by mild to moderate RDS with:

1. Gestational age at birth 34 and 37 weeks of gestation.
2. Diagnosis during the first 24 hours of life, according to clinical and radiological findings.

Exclusion criteria: Any newborn with the following:

1. Gestational age at birth less than 34 weeks or greater than 37 weeks.
2. Major cardiac, respiratory problem.
3. Congenital anomaly, congenital pneumonia.
4. Meconium aspiration syndrome.
5. Polycythemia and hypoglycemia.

Methods:

All the studied groups were submitted to following:

I. Full History taking in delivery room to determine risk factor: Personal history (name, age, sex, address, order of birth, Prenatal history, history of maternal diseases ; asthmatic mother and diabetes, medications taken during pregnancy. Method of delivery normal vaginal delivery or cesarean section, anesthesia during labor, delayed cord clamping, single or multiple births. Duration of delivery, gravity, parity and number of abortion if present, Maturity; Small for gestational age or not. History of resuscitative measures performed after delivery; infants who have natal or prenatal asphyxia, antenatal steroids before elective caesarean section.

II. Clinical Examination: All participants were subjected to the following: 1. Clinical examination: RR, HR, O2 saturation. 2. Scoring of clinical status of the newborn & system of the clinical respiratory status: The scoring system for respiratory distress used in the hospital is:

	0 point	1 point	2 point	3 point
Expiratory grunting	None	Intermittent	Continuous	____
Supraclavicular retraction	None	Mild	Moderate	Severe
Subcostal retraction	None	Mild	Moderate	Severe
Cyanosis	None	At extremities	Central	_____
Nasal flaring	None	Mild	Moderate	Severe

(Malakian et al., 2018)

Level of respiratory Support:

Level	Respiratory support	Oxygen concentration%
1	No oxygen	_____
2	Intra incubator oxygen	30
3	Hood	40
4	Nasal canula	50
5	NCPAP	50- 60

(Malakian et al., 2018)

Investigations: laboratory: Complete blood count, quantitative estimation of CRP, arterial blood gases. Radiological investigations: chest X- ray, lung ultrasound and echocardiography.

Methodology: All studied neonate were calcified randomly into 3 groups each (50 neonate).

Group I: received the ordinary treatment for TTN in form of O2 support, I.V fluid, antibiotics.

Group II: received the ordinary treatment with restriction of fluid intake (50, 65 mL/kg in full term) and (65, 80 mL /kg for preterm neonates).

Group III: received the ordinary treatment plus two doses of Budesonide inhalation 1000µg/dose, 12 h apart, within 6 h after birth).

We Followed up the 3 groups of study for 3 days: Clinically, continuous monitoring by pulse oximetry, ABG, follow up Chest X ray, the outcome of the study (the oxygen needs to maintain the optimum oxygen saturation and PaO2, the length of hospital stay and the incidence of complications in the 3 days at the department of neonatology at Al-Azhar University Hospital and Sohag Teaching Hospital.

Statistical methods:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described

using number and percent. Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR).Significance of the obtained results was judged at the 5% level.

RESULTS

Table (1): Comparison between the three studied groups regarding to demographic data

	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)		p
	No.	%	No.	%	No.	%	
Sex							
Males	32	64.0	34	68.0	32	64.0	0.889
Females	18	36.0	16	32.0	18	36.0	
Gestational age							
Min. – Max.	37.0 – 38.50		37.0 – 39.0		37.0 – 40.0		0.779
Mean ± SD.	37.74 ± 0.51		37.79 ± 0.54		37.85 ± 0.64		
Median (IQR)	37.80 (37.3 – 38.0)		37.80 (37.3 – 38.4)		37.80 (37.3 – 38.4)		
Birth weight							
Min. – Max.	3000.0 – 3780.0		2890.0 – 3780.0		2890.0 – 3780.0		0.882
Mean ± SD.	3397.60 ± 272.26		3375.80 ± 270.26		3376.44 ± 250.61		
Median (IQR)	3500.0 (3200 - 3700)		3400.0 (3100 - 3500)		3400.0 (3200 - 3500)		
Mode of delivery							
NVD	14	28.0	10	20.0	19	38.0	0.137
CS	36	72.0	40	80.0	31	62.0	
Natal or prenatal asphyxia							
No	20	40.0	23	46.0	26	52.0	0.485
Yes	30	60.0	27	54.0	24	48.0	

^{2}: Chi square test, H: H for Kruskal Wallis test

p: p value for comparing between the three groups

Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows that there were insignificant differences between three studied groups regarding Demographic Data (Sex, Gestational age, Birth Weight, Mode of delivery, Asphexia) before intervention.

Table (2): Relation between Mode of delivery and TTN clinical score (before ttt) in each group

TTN clinical score (before)	Mode of delivery		U	p
	NVD	CS		
Group I	**(n = 14)**	**(n = 36)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	212.0	0.356
Mean ± SD.	6.71 ± 0.73	6.94 ± 0.79		
Median	7.0	7.0		
Group II	**(n = 10)**	**(n = 40)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	176.50	0.574
Mean ± SD.	7.10 ± 0.88	6.93 ± 0.80		
Median	7.0	7.0		
Group III	**(n = 19)**	**(n = 31)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	273.50	0.656
Mean ± SD.	6.89 ± 0.81	7.0 ± 0.82		
Median	7.0	7.0		

U: Mann Whitney test
p: p value for comparing between different category
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows that there were insignificant differences between three studied groups regarding to mode of delivery and TTN Clinical Score before intervention.

Table (3): Relation between Neonatal Asphyxia and TTN clinical score (before ttt) in each group

TTN clinical score (before)	Natal or prenatal asphyxia		U	p
	No	Yes		
Group I	**(n = 20)**	**(n = 30)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	250.0	0.290
Mean ± SD.	6.75 ± 0.85	6.97 ± 0.72		
Median(IQR)	6.50	7.0		
Group II	**(n = 23)**	**(n = 27)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	292.50	0.710
Mean ± SD.	6.91 ± 0.79	7.0 ± 0.83		
Median(IQR)	7.0	7.0		
Group III	**(n = 26)**	**(n = 24)**		
Min. – Max.	6.0 – 8.0	6.0 – 8.0	311.50	0.992
Mean ± SD.	6.96 ± 0.82	6.96 ± 0.81		
Median(IQR)	7.0	7.0		

U: Mann Whitney test

p: p value for comparing between different category

Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows that there were insignificant differences between three studied groups regarding to Neonatal Asphyxia and TTN Clinical Score before intervention.

Table (4): Comparison between the three studied groups according to Complete Blood Count (CBC), O_2 saturation

	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)		p
White blood cell count					
Min. – Max.	11.60 – 16.40	10.60 – 17.00	10.50 – 16.40	H= 1.928	0.381
Mean ± SD.	13.97 ± 1.69	13.79 ± 1.69	13.49 ± 1.66		
Median (IQR)	14.60 (12.7 – 15.6)	13.40 (12.5 – 15.0)	13.40 (11.8 – 15.0)		
Hemoglobin					
Min. – Max.	14.60 – 18.70	14.60 – 18.70	14.60 – 18.70	H= 0.687	0.709
Mean ± SD.	16.21 ± 1.18	16.19 ± 1.15	16.29 ± 1.14		
Median (IQR)	15.90 (15.7 – 16.7)	15.90 (15.70 – 16.7)	16.10 (15.7 – 16.7)		
Platlets					
Min. – Max.	200.0 – 281.0	189.0 – 289.0	197.0 – 298.0	F= 2.871	0.060
Mean ± SD.	237.44 ± 21.01	230.94 ± 29.03	242.94 ± 24.51		
Median (IQR)	235.0 (220 – 256)	221.50 (208–260)	241.0 (224–262)		
Oxygen saturation					
Min. – Max.	97.0 – 99.0	97.0 – 99.0	97.0 – 99.0	H= 0.417	0.812
Mean ± SD.	98.24 ± 0.66	98.32 ± 0.65	98.30 ± 0.61		
Median (IQR)	98.0 (98.0 – 99.0)	98.0 (98.0 – 99.0)	98.0 (98.0 – 99.0)		

H: H for Kruskal Wallis test F: F for ANOVA test
p: p value for comparing between the three groups
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows there was insignificant differences between three studied groups as regard WBCs, HB, Plat and O2 saturation according to lab parameters.

Table (5): Comparison between the three studied groups according to TTN clinical score (1st day & 2nd day & 3rd day):

TTN clinical score	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	H	p
Before ttt					
Min. – Max.	6.0 – 8.0	6.0 – 8.0	6.0 – 8.0	0.323	0.851
Mean ± SD.	6.88 ± 0.77	6.96 ± 0.81	6.96 ± 0.81		
Median(IQR)	7.0 (6.0 – 7.0)	7.0 (6.0 – 8.0)	7.0 (6.0 – 8.0)		
1st day					
Min. – Max.	6.0 – 8.0	5.0 – 7.0	5.0 – 7.0	15.816*	<0.001*
Mean ± SD.	6.63 ± 0.60	6.10 ± 0.74	6.24 ± 0.52		
Median(IQR)	6.75 (6.0 – 7.0)	6.0 (6.0 – 7.0)	6.0 (6.0 – 7.0)		
Sig.bet.Grps	p_1<0.001*,p_2=0.002*,p_3=0.497				
2nd day					
Min. – Max.	5.50 – 7.50	4.0 – 7.0	5.0 – 7.0	36.224*	<0.001*
Mean ± SD.	6.47 ± 0.57	5.62 ± 0.67	5.92 ± 0.63		
Median(IQR)	6.50 (6.0 – 7.0)	6.0 (5.0 – 6.0)	6.0 (5.0 – 6.0)		
Sig.bet.Grps	p_1<0.001*,p_2<0.001*,p_3=0.042*				
3rd day					
Min. – Max.	5.0 – 7.0	3.0 – 6.0	4.0 – 7.0	63.006*	<0.001*
Mean ± SD.	6.30 ± 0.58	5.0 ± 0.83	5.34 ± 0.56		
Median(IQR)	6.0 (6.0 – 7.0)	5.0 (4.0 – 6.0)	5.0 (5.0 – 6.0)		
Sig.bet.Grps	p_1<0.001*,p_2<0.001*,p_3=0.151				

H: H for Kruskal Wallis test, Pairwise comparison bet. each 3 groups was done using Post Hoc Test (Dunn's for multiple comparisons test)
p: p value for comparing between the three groups
p1: p value for comparing between Group I and II
p2: p value for comparing between Group I and III
p3: p value for comparing between Group II and III
p4: p value for Wilcoxon signed ranks test for comparing between before and after 1st day & 2nd day & 3rd day
*: Statistically significant at $p \leq 0.05$
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows there is significant difference as regarding TTN clinical score between the three groups after treatment and also significant improvement in the score from 1st & 3rd day after treatment in the group received restricted fluid than other groups followed by ordinary treatment group then inhaled budesonide group.

Table (6): Comparison between the three studied groups according to respiratory and heart rate

		Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	H	P
Respiratory rate	**Before ttt**					
	Min. – Max.	67.0 – 78.0	65.0 – 78.0	65.0 – 78.0	1.296	0.523
	Mean ± SD.	73.56 ± 3.99	73.14 ± 4.10	72.98 ± 3.97		
	Median (IQR)	75.50 (70.0 – 77.0)	75.0 (70.0 – 77.0)	75.0 (70.0 – 76.0)		
	After ttt					
	Min. – Max.	66.0 – 75.0	55.0 – 70.0	55.0 – 70.0	101.013*	<0.001*
	Mean ± SD.	72.22 ± 3.25	63.16 ± 3.27	64.32 ± 2.40		
	Median (IQR)	74.0 (70.0 – 75.0)	65.0 (60.0 – 65.0)	65.0 (65.0 – 65.0)		
	Sig. bet. Grps	$p_1<0.001^*, p_2<0.001^*, p_3=0.322$				
Heart rate	**Before ttt**					
	Min. – Max.	127.0 – 138.0	123.0 – 145.0	127.0 – 145.0	0.396	0.820
	Mean ± SD.	134.24 ± 3.06	134.26 ± 3.40	134.80 ± 2.57		
	Median (IQR)	135.0 (134.0 – 135.0)	135.0 (133.0 – 135.0)	135.0 (134.0 – 135.0)		
	After ttt					
	Min. – Max.	128.0 – 137.0	121.0 – 137.0	123.0 – 137.0	6.446*	0.040*
	Mean ± SD.	132.96 ± 2.78	130.96 ± 4.06	131.64 ± 3.60		
	Median (IQR)	133.0 (132.0 – 135.0)	132.0 (130.0 – 134.0)	132.0 (130.0 – 134.0)		
	Sig. bet. Grps	$p_1=0.013^*, p_2=0.088, p_3=0.439$				

H: H for Kruskal Wallis test, Pairwise comparison bet. each 3 groups was done using Post Hoc Test (Dunn's for multiple comparisons test)
p: p value for comparing between the three groups
p1: p value for comparing between Group I and II
p2: p value for comparing between Group I and III
p3: p value for comparing between Group II and III
p4: p value for Wilcoxon signed ranks test for comparing between before and after
*: Statistically significant at $p \leq 0.05$
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows that there was insignificant differences between three studied groups as regard pretreatment RR, HR but as regard post treatment score there was significant improvement in group received restricted fluid than other groups followed by ordinary treatment group then inhaled budesonide group.

Table (7): Comparison between the three studied groups according to Arterial Blood Gas

		Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	H	P
FiO2	**Before ttt**					
	Min. – Max.	45.0 – 76.0	40.0 – 76.0	40.0 – 76.0	2.930	0.231
	Mean ± SD.	62.32 ± 10.55	61.40 ± 10.08	59.06 ± 10.82		
	Median (IQR)	60.0 (55.0 – 70.0)	60.0 (55.0 – 70.0)	56.0 (50.0 – 70.0)		
	After ttt					
	Min. – Max.	44.0 – 76.0	28.0 – 46.0	28.0 – 46.0	94.285*	<0.001*
	Mean ± SD.	61.44 ± 10.65	37.66 ± 4.82	37.14 ± 4.25		
	Median (IQR)	60.0 (54.0 – 69.0)	36.0 (34.0 – 43.0)	36.0 (34.0 – 40.0)		
	Sig. bet. Grps	$p_1<0.001^*, p_2<0.001^*, p_3=0.854$				
PaO2	**Before ttt**					
	Min. – Max.	44.0 – 57.0	40.0 – 57.0	40.0 – 57.0	4.186	0.123
	Mean ± SD.	52.90 ± 4.93	52.24 ± 5.23	51.54 ± 5.53		
	Median (IQR)	55.0 (46.0 – 57.0)	55.0 (50.0 – 56.0)	54.50 (45.0 – 56.0)		
	Sig. bet. Grps	$p_1=0.015^*, p_2=0.002^*, p_3=0.554$				
	After ttt					
	Min. – Max.	45.0 – 57.0	65.0 – 89.0	65.0 – 89.0	100.691*	<0.001*
	Mean ± SD.	53.24 ± 3.89	78.42 ± 6.75	76.56 ± 7.74		
	Median (IQR)	54.50 (53.0 –56.0)	78.0 (76.0 – 86.0)	75.0 (70.0 – 86.0)		
	Sig. bet. Grps	$p_1<0.001^*, p_2<0.001^*, p_3=0.328$				
PaCO2	**Before ttt**					
	Min. – Max.	45.0 – 52.0	43.0 – 52.0	40.0 – 52.0	4.264	0.119
	Mean ± SD.	47.0 ± 2.15	47.0 ± 2.40	46.14 ± 2.68		
	Median (IQR)	46.0 (46.0 – 48.0)	46.0 (45.0 – 48.0)	45.50 (45.0 – 48.0)		
	After ttt					
	Min. – Max.	44.0 – 51.0	38.0 – 46.0	38.0 – 46.0	75.490*	<0.001*
	Mean ± SD.	46.50 ± 2.22	42.84 ± 1.49	43.30 ± 1.52		
	Median (IQR)	45.0 (45.0 – 47.0)	43.0 (42.0 – 44.0)	43.50 (43.0 – 44.0)		
	Sig. bet. Grps	$p_1<0.001^*, p_2<0.001^*, p_3=0.139$				
PH	**Before ttt**					
	Min. – Max.	7.33 – 7.31	7.33 – 7.31	7.33 – 7.32	1.886	0.389
	Mean ± SD.	0.01 ± 7.32	0.01 ± 7.31	0.01 ± 7.32		
	Median (IQR)	50.0 (7.3 – 7.32)	50.0 (7.30 – 7.32)	50.0 (7.31 – 7.32)		
	After ttt					
	Min. – Max.	7.30 – 7.32	7.30 – 7.39	7.30 – 7.39	39.754*	<0.001*

	Mean ± SD.	7.31 ± 0.01	7.34 ± 0.03	7.34 ± 0.03		
	Median (IQR)	7.30 (7.30–7.31)	7.35 (7.31–7.37)	7.34 (7.31– 7.36)		
	Sig. bet. Grps	p1<0.001*,p2<0.001*,p3=0.515				

H: H for Kruskal Wallis test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test)
p: p value for comparing between the three groups
p1: p value for comparing between Group I and II
p2: p value for comparing between Group I and III
p3: p value for comparing between Group II and III
p4: p value for Wilcoxon signed ranks test for comparing between before and after
*: Statistically significant at $p \leq 0.05$
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

This table shows there was significant improvement between the three studied groups as regard FIO_2, Pao_2 and $paCO_2$ and Ph after treatment in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group.

Table (8): Comparison between the three studied groups according to duration of hospitalization

Duration of hospitalization	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	H	p
Min. – Max.	2.0 – 8.0	2.0 – 6.0	2.0 – 6.0	24.728*	<0.001

Mean ± SD.	4.36 ± 1.57	3.0 ± 1.07	3.10 ± 0.99		*
Median(IQR)	4.50 (3.0 – 6.0)	3.0 (2.0 – 3.0)	3.0 (2.0 – 4.0)		
Sig.bet.Grps	$p_1<0.001^*$,$p_2<0.001^*$,$p_3=0.535$				

H: H for Kruskal Wallis test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test)
p: p value for comparing between the three groups
p1: p value for comparing between Group I and II
p2: p value for comparing between Group I and III
p3: p value for comparing between Group II and III
*: Statistically significant at $p \leq 0.05$
Group I: Oxygen, Group II: Restrictive fluid, with o_2 Group III: Inhaled Budesonide, with o_2

Duration of hospitalization was shorter in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group with significant differences.

DISCUSSION

Transient tachypnea in the newborn, also known as wet lung or type II respiratory distress syndrome, is one of the common respiratory problems in the neonates, which is the cause for a great number of hospitalizations in the Neonatal Intensive Care Unit (NICU).It separates the neonate from the parents and deprives the neonate from breastfeeding. Transient tachypnea in the neonate is usually a benign syndrome, which increases the respiratory rate to 60 breaths per min instantly after birth, and rarely causes problems, such as hypoxemia (i.e., an abnormally low concentration of oxygen in the blood), respiratory failure, and death **(Akbarian et al., 2018)**.

Although TTN is a self-limiting condition that usually leaves no sequelae, tachypnoea may interfere with enteral feeding; may require testing and close monitoring along with oxygen therapy; and may be a cause of great concern for parents. Studies have shown an association between TTN and asthma, bronchiolitis, and other wheezing syndromes later in life, as well as persistent pulmonary hypertension in rare cases **(Bruschettini et al., 2020)**.

In the current study we aimed to study the effect of Restrictive Fluid Management versus early Budosonide inhalation in outcome of Transient Tachypnea of the Newborn and on the hospital course of neonates with (TTN).

In the current study there were insignificant differences between three groups as regard demographic data, white blood

cell count, hemoglobin level, oxygen saturation, APGAR score.

In agreement with our result **Sardar S et al.,** compared cases received restricted fluid versus whom received ordinary treatment and found that Overall, both groups were similar in every aspect, except that more babies in the restricted arm had 5 minutes Apgar of ≥8 (97.82% vs 84.78%, p = 0.026 **(Sardar et al., 2020)**.

Akbarian et al., 2018, enrolled late preterm, term, and post-term neonates with TTN. The diagnosis of TTN was based on the presence of tachypnea (respiratory rate > 60 per minute) and at least one radiological sign suggestive of the diagnosis. If chest X-ray was normal, the diagnosis of TTN was made if the Silverman Anderson score for respiratory distress was 4 or greater and the neonate was hospitalized within six hours of birth **(Silverman and Andersen, 1956)**.

Neonates in the restricted fluid group received 50 mL/kg if born at term or post-term gestation, and 65 mL/kg if born at late preterm gestation. Neonates in the standard fluid group received 65 mL/kg if born at term or post-term gestation, and 80 mL/kg if born at late preterm gestation. Fluid intake was increased by 20 mL/kg every subsequent day to reach a maximum of 150 mL/kg in term and post-term neonates, and 180 mL/kg **(Sharma, 2017)**.

Elfarargy et al., agree with our result as found that revealed that there was no significant difference in examined neonates regarding weight, gestational age, mode of delivery, gender, and APGAR score **(Elfarargy et al., 2020)**.

Another study comparing inhaled steroid with ordinary treatment found that there was no significant difference regarding demographic characters between both groups **(Bakry et al., 2019)**.

In the current study there was insignificant differences between three groups as regard pretreatment TTN clinical score RR, HR but as regard post treatment score there was significant improvement in group received restricted fluid than other groups followed by ordinary treatment group then inhaled Budesonide group.

Elfarargy MS et al., demonstrated no benefit of inhaled budesonide over placebo in treatment of TTN regarding TTN clinical score, and SpO2 although no difference was found regarding PH and the significant effect of it was better clinically than the placebo group and this explained our result. These results could be

due to delayed effect of steroid **(Elfarargy et al., 2020)**.

On the other hand Another study comparing inhaled steroid with ordinary treatment found that after management there was significant decrease (P< 0.001) in respiratory rate which is 64.80 (± 4.14) in Budesonide 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 Budesonide group versus 7.32±0.85 in control group 4 hours after enrollment in study differences with our study due to they measured after several hours of treatment as the effect of steroids appear **(Bakry et al., 2019)**.

Stroustrup et al., 2012 mentioned that fluid restriction did not cause adverse events or unsafe dehydration. Fluid management strategy did not affect primary or secondary outcomes in the total study population. Fluid restriction significantly reduced the duration of respiratory support (P =.008) and hospitalization costs (P =.017) in neonates with severe TTN **(Stroustrup et al., 2012)**.

Korean study done by **Kim et al., 2014** reported that the duration of supplemental oxygen therapy and the duration of empiric antibiotic treatment were significantly shorter in the Budesonide treated group with P value <0.01 and 0.04 respectively. The duration of tachypnea was shorter in patients receiving inhalational Budesonide therapy, although this difference was not statistically significant P=0.37.

As regard FIO_2, Pao_2, $paCO_2$ and PH there was significant improvement after treatment in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group. This proved by study comparing inhaled steroid with ordinary treatment found that No significant difference between both groups (steroid group and control) regarding blood gases **(Bakry et al., 2019)**.

There were insignificant differences between three groups as regard pre and post treatment serum potassium and serum glucose. This goes with **Sardar, 2020; Stroustrup, 2012** as in the pooled incidence of hypoglycemia was comparable in the two groups (RR 1.00, 95% CI 0.15 to 6.82; RD 0.00; 95% CI: 0.05 to 0.05) **(Sardar et al., 2020**; **Stroustrup et al., 2012)**.

Another study comparing inhaled steroid with ordinary treatment found that there was No significant difference between both groups regarding blood gases, serum K and blood glucose

data on Admission **(Bakry et al., 2019)**.

In the current study duration of hospitalization was shorter in fluid restriction group than other groups followed by ordinary treatment group then inhaled Budesonide group with significant differences.

In agreement with our result the data from **Eghbalian, 2018** show a significantly lower duration of hospitalization in the restricted fluids group (MD - 0.92 days, 95% CI -1.53 to -0.31 days) **(Eghbalian et al., 2018)**.

Armangil D et al., 2011 found no significant difference in total duration of respiratory support in hours between Budesonide group (median=30) and control group (median=48) with P =0.112. But, the total duration of hospitalization in days was significantly shorter in Budesonide group (median=4) than in control group (median=6) with P= 0.002 **(Armangil et al., 2011)**.

As regard need for MV or oxygen therapy there was insignificant differences between three groups.

On the other hand **Sardar S et al.,** showed that Regarding the primary outcome, babies in the restricted arm required CPAP for significantly less duration compared with those in the standard arm v=(48[42,54] hrs 54[48,72] hr, p = 0.002). However, the incidence of CPAP failure (4.34%) in the restricted arm vs (6.52%) in the standard arm, p = 0.645 and post- CPAP O 2 requirement were not different **(Sardar et al., 2020)**.

Eghbalian, 2018 and **Sardar, 2020** show no significant difference in duration of oxygen therapy between the two groups (group with restricted fluid and group with ordinary treatment) (mean difference [MD] - 12.95 hours, 95% confidence interval [CI] -32.82 to 6.92 hours) **(Eghbalian et al., 2018** and **Sardar et al., 2020)**.

As regard Need for invasive ventilation three trials reported this outcome **(Akbarian et al., 2018**; **Eghbalian et al., 2018** and **Sardar et al., 2020)**. The pooled incidence was comparable in two groups (RR 0.73, 95% CI 0.24 to 2.23; RD -0.02; 95% CI: -0.07 to 0.04).

Elfarargy et al., showed that the inhaled steroid group was better placed than the placebo group as there were lower number of neonates who need CPAP in this group, although this difference was no significant. In addition, the inhaled steroid group was significantly better than

placebo group regarding the duration of hospital stay. There was significantly lower duration of stay of neonates in incubator in the inhaled steroid group compared with the placebo group **(Elfarargy et al., 2020)**.

CONCLUSION

The present study demonstrated that the restrictive fluid management can decrease the hospitalization period, respiratory support period, and the respiratory distress score in the neonates with transient tachypnea, and was better than ordinary treatment and steroid inhalation in the form of Budosonide inhalation. Fluid restriction appears safe in late preterm and term neonates with uncomplicated TTN. Early inhaled budesonide steroid was associated with improvement in respiratory functions, decreasing the signs of respiratory distress and significantly reducing the TTN clinical manifestations in term neonates suffering from TTN.

RECOMMENDATIONS

In the present study, restrictive fluid restriction can be attempted alone to decrease the duration of hospital stay and the severity of TTN and to improve neonatal outcome. Further larger scale studies are necessary to confirm the safety of inhaled Budesonide in this common respiratory condition. Further studies are necessary to show efficacy of early use of admission to NICU due to TTN. Respiratory morbidity is more common in infants delivered by elective caesarean section compared to intended vaginal delivery even in term infants. Therefore, delaying elective C.S until 39 weeks or later is recommended.

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