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Comparison of Restricted Fluid Volume with Standard Fluid Volume in Management of Transient Tachypnea of the Newborns: A Randomized Controlled Trial

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Abstract

Background: Transient tachypnea of the newborn (TTN) is one of the most common neonatal respiratory disease and its symptoms usually begins in the first few hours after birth. The volume of fluid intake according to the neonate's conditions varies. We aimed to compare the restricted fluids volume with standard fluids volume in treatment of neonates with TTN.

Materials and Methods: This clinical trial was performed on 80 neonates with a diagnosis of TTN admitted in the Neonatal intensive care unit (NICU) of Fatemiyeh Hospital and Beasat Hospital of Hamadan Medical University in Iran. Patients were randomly divided to standard fluids volume (control = 40), and restricted fluids volume treatment groups (case = 40). The hospitalization duration, oxygen therapy duration as well as the number of days need for oxygen with hood; Nasal continuous positive airway pressure (NCPAP), and mechanical ventilation therapy was recorded. After data collection, the data were statistically analyzed via SPSS software (version 21.0).

Results: The subjects were 30 (37.5%) females and 50 (62.5%) males (62.5%) with an average gestational age of 38.12 (±1.07) weeks. The main aim from this interventional study was effect of restricted fluid therapy on management of TTN in NICU section. The hospitalization duration, oxygen therapy duration and need for oxygen therapy with hood in the intervention group were significantly lower than the control group ($P<0.05$), but need for mechanical ventilation and need for NCPAP were not significantly different between the two groups ($P>0.05$).

Conclusion

TTN treatment with restricted fluids volume, compared with standard volume of fluids, significantly reduces the need for respiratory supports as well as the duration of hospitalization in the NICU section.

Key Words: Restricted fluids volume, Standard fluids volume, Transient tachycardia of the newborn**.**

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1- INTRODUCTION

Maintaining and improving neonatal health has a special importance in health care services. Neonates undergo a lot of physiological changes, immediately after birth. This course of life is associated with high mortality and morbidity. Most neonatal deaths occur in the first 24 hours after birth (1). Approximately, 7 million neonates die every *year* in first 28 days of life. According to the latest data in Iran, neonatal mortality rate is 17.66 per 1,000 live births (1). Respiratory problems in neonates are among the common causes of death (2). Transient tachypnea of the newborn (TTN) and respiratory distress syndrome (RDS) are the most common respiratory diseases in the neonates (3).

TTN, also called type II respiratory distress syndrome, occur in 0.5 to 2.8% of all live births (4, 5). This condition is common in term neonates born with cesarean section delivery. Other risk factors for TTN include: neonates of *asthmatic* and diabetic mothers, preterm neonates, male gender, neonatal asphyxia, neonates with gestational age of 39 and newborns with respiratory muscle weakness due to passing the sedative drugs across the placenta (6-9).

Fetal lung fluid is secreted by the alveolar cells and is responsible for the natural development of fetus lung. At birth, increasing levels of mediators such as epinephrine and glucocorticoids upregulates Amiloride sensitive sodium channels (ENaC) on the apical side of the lung epithelial cells and leads to absorption of sodium and water from the alveolar to interstitial space (10-12). TTN is an obstructive disease caused by delayed absorption of fluid from newborn's lung (13). After birth, continued presence of fluid in the alveoli space reduces the lung capacity and tidal volume. It also increases the volume of dead space and finally leads to respiratory distress (13-15). This condition leads to accumulation of fluid in peribronchial space and compression of bronchioles and airy lungs (14). The diagnosis of neonatal transient tachypnea usually involves rule out of other causes, and there is no specific test for diagnose it (14). The symptoms of TTN are self-limited and usually resolved in the first few hours after birth (6). However, it is responsible for majority of neonate admissions in NICU section (16). Admission in NICU leads to delay in breastfeeding and establishment of mother-child relationship; which, in addition to social effects, causes a financial burden on the family. These psychosocial and financial consequences could be more important with increasing rate of preterm births, elective cesarean sections and high-risk newborns for TTN (17, 18).

Therefore, treatment of TTN is especially important. The only treatment for TTN is supportive care. This includes oxygen therapy, stop enteral feeding, initiation of intravenous fluids and mechanical ventilation in rare cases; any intervention that accelerates fetal lung fluid clearance can reduce length and severity of symptoms. This finally leads to reducing need for respiratory support and hospitalization duration. The use of oral, injectable or inhaled drugs does not any significant effect on disease outcomes and more studies is needed in this field (6).

In the traditional method(standard), infants received 60, 80 and 100 ml/kg/day fluid in the first, second and third days after birth, respectively (19). Healthy newborns who are exclusively breastfed receive less than fluids in compared with respiratory distress or other conditions that are prescribed intravascular fluids; because only a small amount of milk is secreted in breast in the first days of birth. Therefore, it is hypothesized that restricting fluid intake in the first three to five days after the birth of newborns with TTN mimics the normal physiological conditions existing in healthy neonates. As a result,

symptoms can be resolved faster (20). In one study, epinephrine was used for management of TTN (24); in other study, salbutamol was used for management of TTN (25). Also, based on studies, restricted fluid volume can reduce the risk of necrotizing enterocolitis and ductus arteriosus (6, 19, 20). Therefore, the aim of this study is comparing the restricted fluid volume with standard fluid volume in treatment of transient tachypnea of the newborn.

2- MATERIALS AND METHODS

2-1. Subjects

This clinical trial study was performed on newborns with diagnosis of TTN at neonatal intensive care unit of Besat and Fatemieh Hospitals, teaching care medical centers in Hamadan city, Iran during 2016 to 2017. The TTN was diagnosed with following conditions: 1- respiratory rate more than 60 per minute (tachypnea), 2- continuity of tachypnea for at least 12 hours, 3- prominent central pulmonary vessels or thickening of interlobar fissures in chest X-ray (CXR), and 4- respiratory alkalosis in arterial blood gas (ABG) test. Inclusion criteria were as follows:

1- Neonates with gestational age 37 to 41, and 2- neonates who were hospitalized in the first three days of their life; patients with following criteria were excluded from study: 1- congenital anomalies, 2- proved systemic infection (positive blood culture), 3- meconium aspiration, 4- respiratory distress syndrome (according to CXR), 5- intrauterine growth retardation, 6- pneumonia, 7- congenital heart disease, 8- multiple organ failure, 9- disseminated intravascular coagulation, 10- hypocalcemia, 11- hypoglycemia, 12- polycythemia, 13- serum sodium levels more than 150 meq/l, 14- blood urea nitrogen levels more than 20 mg/dl, 15- serum potassium levels of greater than 5 meq/l, and 16- urine output less than 1 cc/kg/hour. Also, patients were excluded from study if their blood urea nitrogen (BUN) and creatinine levels were increased or their urine output reduced to lower than 1 cc/kg/hour during the study.

2-2. Study design

Sample size was calculated by considering 95% confidence level (CI) and 80% power of test. According to a pervious study (19), the difference in admission duration between two groups was 1.25 days and standard deviation of admission duration in two groups was 2.0 and 2.2 day, respectively. Finally, sample size was determined 40 neonates in each group. The neonates were allocated in two groups by block randomization with randomly selected block size of 4. Briefly, before selection of patients a table of 10 random blocks was prepared which blocks were include two "A" (control) letter and two "B" letter (intervention). The sequence of these letters was randomly limited and obtained table showed how people should be assigned to the two groups.

2-3. Treatments

Patients were selected based on inclusion and exclusion criteria and randomly divided into two groups (intervention and control). After taking the informed consent from neonate's parents, the patients in intervention and control group were treated with restricted fluids volume and standard fluids volume respectively as below:

Intervention group: received 40, 60 and 80 ml/kg/day of dextrose 10% solution at first, second and third day of life, respectively. Also, Sodium chloride 3 mEq/kg/day and potassium chloride 2 mEq/kg/day was prescribed for patients from the second day of life.

Control group: received 60, 80 and 10 ml/kg/day of dextrose 10% at first, second and third day of life, respectively. Also, Sodium chloride 3 mEq/kg/day and potassium chloride 2 mEq/kg/day was prescribed for patients from the second day of life. It is worth mentioning, 20 ml/kg/day of dextrose 10% was added to solution if patients were under a radiant warmer. Finally, the patients' outcome (final response) was assessed. Duration of hospitalization, as well as duration of need for oxygen therapy with hood, nasal CPAP and mechanical ventilation was recorded as the final response to the treatments. In this study, the decision to initiate or terminate respiratory support was carried out by individuals who did not know about patient's allocation.

2-4. Statistical analysis

Quantitative values are presented as mean and standard deviation qualitative values are presented as frequency and percent. Comparison of quantitative and qualitative variables between two groups were performed using independent t-test (or Mann Whitney U test), and Chi-square test, respectively. All analyses were performed using SPSS software version 21.0 and $P<0.05$ was considered as statistically significant.

2-5. Ethical Considerations

Informed consent was obtained from all parents of patients. Also, this study was approved by the ethics committees of Hamadan University of Medical Sciences (IR.UMSHA.REC.1395.153) and registered in Iranian Registry of Clinical Trials (IRCT20120925010933N10).

3- RESULTS

In this research 80 neonates, contains 50 males and 30 females, with TTN were included in study. The average of gestational age and birth weight of participants was 38.12 (±1.07) and 3.37 (±0.37), respectively. Sex distribution, gestational age and birth weight of participants were compared between two groups. Sex distribution and gestational age of the two groups were compared with Chi-square test and results are presented in **Table.1**. The sex distribution of patients showed significant differences between two groups ($P<0.05$); while gestational age of two groups showed no significant differences in the mean ($P>0.05$). Independent t-test showed that two groups are similar in term of birth weight ($P>0.05$) (**Table.2**).

Table-1: Comparison of sex distribution and gestational age between the groups.

Variables		Frequency (Percent)		Chi-square test (X^2)
		Intervention group	Control group	
Gender	Male	30(75)	20(50)	P=0.021 df=1 X^2=5.33
	Female	20(50)	10(25)	
Gestational age*	37 weeks	10(25)	14(35)	P=0.574 df=2 X^2=1.11
	38 weeks	20(50)	16(40)	
	39 weeks	8(20)	1(2.5)	
	40 weeks	2(5)	6(15)	
	41 weeks	0(0)	3(7.5)	

* To calculate the Chi-square, the gestational age of 39 weeks and later were combined.

Table-2: Comparison of birth weight between the groups.

Groups	Birth weight Mean ± Standard deviation	t-test
Control	3.36(±0.46)	P=0.806 df=78 t=0.246
Intervention	3.38(±0.30)	

The mean of hospitalization and oxygen therapy duration were compared between the groups using Mann Whitney U test. Based on the test results, hospitalization and oxygen therapy duration in intervention group were significantly lower than control group (P<0.05) (**Table.3**).

Table-3: Comparison of duration of hospitalization and oxygen therapy between the groups.

Variables	Intervention group			Control group			Mann Whitney u test
	Minimum	Maximum	Mean(±SD)	Minimum	Maximum	Mean(±SD)	
Duration of hospitalization (day)	1	7	4.18(±1.53)	2	7	5.10(±1.25)	P = 0.002
Duration of oxygen therapy (day)	1	4	1.38(±0.667)	1	4	2.5(±0.816)	P < 0.001

SD: Standard deviation.

In **Table.4** need for oxygen therapy with hood, nasal CPAP and mechanical ventilation are compared between two groups by chi-square test. The statistical test results showed that oxygen therapy with hood, nasal CPAP and mechanical ventilation were needed more in control group, in compared with intervention group. The mean duration of need for oxygen therapy with hood was 1.23(±0.48) and 2.20(±0.608) days in intervention and control group, respectively. Nasal CPAP was needed for 0.13(±0.404) days in intervention group and 0.25(±0.439) days in control group. Also, the need for mechanical ventilations in intervention group was lower than control group, 0.03 vs. 0.05 days.

Table-4: Comparison of need for oxygen therapy with hood, nasal CPAP and mechanical ventilation between the groups.

Variables		Intervention group Frequency(Percent)	Control group Frequency(Percent)	Chi-square test **(X^2)**
Need for oxygen therapy with hood	1 day	32(80)	4(10)	P = 0.021 df=1 X^2=5.33
	2 days	7(17.5)	24(60)	
	3 days	1(2.5)	12(30)	
Need for nasal CPAP	Yes	4(10)	10(25)	P = 0.077 df=1 X^2=3.12
	No	36(90)	30(75)	
Need for mechanical ventilation	Yes	1(2.5)	2(5)	P = 0.556 df=1 X^2=0.35
	No	39(97.5)	38(95)	

4- DISCUSSION

In this study, restricted fluid volume was compared with standard fluid volume for the treatment of TTN (19). One of the important findings in this study was the reduction of the hospitalization duration in intervention group (4.18 days) compared to control group (5.5 days). According to a study by Riskin et al., any factor that delayed the onset of enteral feeding, would prolong hospitalization time (14). Based on Kao et al., and Gupta et al., studies, any intervention that increases lung fluid clearance and decreases the duration of symptoms will reduce the length of hospitalization and ultimately reduce the costs (6, 21). So it seems, restricted fluid volume in TTN treaemnt has accelerated the pulmonary fluid clearance in neonates. Dehdashtian et al., has been reported that duration of hospitalization between the intervention and control groups is not significant. It may be related to delay in iniation of enteral feeding and hyperbilirubinemia (19).

Stroustrup et al,. showed that fluid restriction is a safe method and can significantly reduce the hospitalization charges, because of reduction in the length of hospital stay (22). In this study, 90% of infants in the control group needed 2-3 days of oxygen therapy with hood, while 80% of the newborns in the intervention group needed oxygen therapy with hood for only one day. Also, the mean duration of oxygen therapy was significantly lower in intervention group (1.38 day) compared to control group (2.5 day). In Stroustrup et al.'s study, there was no significant difference in total duration of respiratory support between the intervention group and standard group. In severe TTN, respiratory support duration in intervention group were significantly lower than the control group (22). In similar to our study, Dehdashtian et al., reported that duration of oxygen therapy in the intervention group was significantly lower than the control group (19). Therefore, it can be concluded that reduction in need to oxygen therapy may be due to decrease in severity of symptomes. This may be caused by increase in pulmonary fluid absorption, because hasten of remaining pulmonary fluid absorption will reduce the severity of symptoms (23). In present study, the need for NCPAP and mechanical ventilation in the intervention group was lower than of the control group, but no significant difference was present between two groups. In consistent to our study, dehdashtian et al., have been reported that difference between groups for need to mechanical ventilation was not statistically significant; while a significant difference in number of cases need to NCPAP, was presented between groups.

The effect of fluid volume restriction on reducing need to NCPAP in newborn with TTN is not yet clear (19). In summary, restricted fluids volume is a mimic of normal physiological condition in first days of life (19). Increased fluids volume in polmunary interstitium can result from increased pulmonary venous pressure or increased lung blood flow. In these circumstances, received fluid volume is restricted. Likewise, in TTN, fluid volume in lung interstitium is increased,when alveolar fluid is absorbed through the lymphatic vessels. Therefore, restriction of fluids volume in the first days of life may accelerate drainage of fluids into the vascular network (6).

4-1. Limitations of the study

Some of parents had little cooperation and we had to satisfy them to do this interventioal study. Another problem was afew number of patients in one of the two hospitals.

5- CONCLUSION

Based on our findings, restriction of fluid volume in neonates with TTN (in the first three days of life) will reduce the

hospitalization, oxygen therapy duration and need for oxygen therapy with hood. So, this intervention is an effective therapeutic approach to reduce symptoms and increase lung fluid clearance.

6- CONFLICT OF INTEREST: None.

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