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Therapeutic effect of inhaled budesonide in transient tachypnea of newborn: A placebo-controlled study

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ABSTRACT

Transient tachypnea of the newborn (TTN) is a chest disease found in neonates. It varies from mild to severe and is accompanied by neonatal morbidity and respiratory complications. This is a prospective placebo-controlled study, identification number is TCTR20200513005, which was done in the neonatal unit of Tanta University Hospital between June 2016 and March 2018. This study comprised 100 neonates with TTN, which were divided into two groups. The first group (inhaled steroid group) consisted of 50 neonates with TTN who were exposed to inhalation of corticosteroids (budesonide 2 ml, 0.25 mg/ml suspension for nebulizer, AstraZeneca AB, Södertälje, Sweden), the first dose was administered within 6 h of birth and the second dose was given 12 h later. The second group (placebo group) consisted of 50 neonates with TTN who were exposed to placebo inhalation (2 ml of distilled sterile water). There was significant difference between both groups regarding Down score (P = 0.001), TTN clinical score (P = 0.001) and Saturation of Peripheral Oxygen (SpO_2) measured by pulse oximeter (P = 0.008), while there was nonsignificant difference between both groups regarding PH (P = 0.573), and this showed that clinically the inhaled steroid group is significantly better than the placebo group. Hence, this study concludes that since administration of inhaled budesonide showed improvement in TTN cases, it could be a recommended line of treatment for neonatal TTN.

Keywords: *newborn, inhaled, budesonide, tachypnea*

INTRODUCTION

Transient tachypnea of the newborn (TTN) is considered as one of the most common respiratory disorders affecting 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. This in mild cases is considered a self-limiting disease, while in severe cases may lead to acute manifestation of respiratory distress (tachypnea, sever retraction, audible grunting and cyanosis in cases with severe form of TTN). Further, in acute cases this could lead to fatigue and exhaustion of respiratory muscles with impending respiratory failure unless respiratory support is provided through nasal cannula, or mechanical ventilator.[1,2]

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 CO_2.[3]

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.[3]

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.[4]

Treatment of TTN varies according to its severity, as in mild cases it is a self-limiting disease. However, some studies have questioned the role of steroids in the in reversal of the pathogenesis of this disease. Hence, further researches are needed to clarify the role of steroids, especially the inhaled steroids in the management of TTN.[5]

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.[6]

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.[6]

Treatment of TTN decreases mortality, which occurs due to the long stay of neonates in incubator. This further increases the chances of developing malignant TTN or secondary bacterial infection, leading to neonatal pneumonia and sepsis.[6]

This study is aimed to show whether early inhaled corticosteroids improve respiratory distress and manifestation of TTN in term neonates with TTN.

PATIENTS AND METHODS

This was a prospective placebo-controlled study, identification number is TCTR20200513005, done in the neonatal unit of Tanta University hospital between June 2016 and March 2018. The study was approved by the ethical committee. Parents of all neonates had signed informed consent.

TTN CLINICAL SCORE

TTN clinical score was done for all neonates comprising the study based on Armangil et al.[7]

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TTN clinical score consists of the following four items: respiratory rate, retractions, grunting, and nasal flaring.

Inclusion Criteria

Full-term neonates (>37 weeks) and diagnosis of TTN as defined by Armangil et al.[7] and Riskin et al.:[8] (1) Tachypnea (respiratory rate [RR] ≥ 60 b/min) within 6 h after delivery with a required FiO_2 >0.25; (2) persistent tachypnea for at least 4 h; (3) chest X-ray showing one of the following: evident pulmonary vascular markings, increased interlobar fissures with evident fluid, or symmetrical congested perihilar tissues; (4) the clinical picture and X-ray findings are self-limited and transient and disappear within the first 7 days of life.

Exclusion Criteria

Respiratory distress syndrome, meconium aspiration syndrome, non-respiratory causes of respiratory distress (congenital heart disease, polycythemia, and hypoglycemia), neonatal pneumonia, neonatal sepsis, and prenatal steroids.

Study Population

Initially, this research comprised 74 patients in the first group (inhaled steroid group), of which 24 cases were excluded as they were not diagnosed with TTN (e.g., RDS or neonatal pneumonia), and 71 patients in the second group, of which 21 cases were excluded as they were also not diagnosed with TTN (e.g., RDS or neonatal pneumonia). Finally, each group comprised 50 TTN patients.

Drug Administration

This study was done with 100 neonates diagnosed with TTN. It was divided into two groups, each group having 50 neonates. Both groups were put on similar nasal cannulas with the same flow of oxygen(2L/min) so to give the same FiO2. The 1st group (inhaled steroid group) was exposed to inhalation of corticosteroids (budesonide 2 ml, 0.25 mg/ml suspension for nebulizer; AstraZeneca AB, Södertälje, Sweden) to ensure adequate, therapeutic and safe dose to overcome the low lung deposition of drugs given by inhalation to infants.[9] Inhalations were provided through a face mask in addition to 2 ml of 0.9% saline. The first dose was administered within 6 h of birth and the second dose after 12 h. This was similar to the studies done on the same topic, but used budesonide 2 ml = 1,000 μg.[10] Some studies used 800 μg of budesonide per day for 2 weeks, or 400 μg of budesonide daily until discontinuation of oxygen therapy.[11] Patients in the 2nd group (placebo group) were exposed to inhalation of placebo (2 ml of distilled sterile water).

TTN clinical score was done for all neonates comprising the study based on Armangil et al.[7] TTN clinical score consists of the following four items: respiratory rate, retractions, grunting, and nasal flaring.

Respiratory rate: If the respiratory rate is below 60 breaths/min, then the score will be 0; if it is 60–100 breaths/min, the score will be 1, and if it is more than 100 breath/min, then the score will be 2.

Retractions: If there is no retraction, the score will be 0; if there is intermittent retraction, the score will be 1; and if there are continuous retractions, then the score will be 2.

Grunting: If there is no grunting, the score will be 0; if there is intermittent grunting, the score will be 1; and if there is continuous grunting, then the score will be 2.

Nasal flaring: If there is no nasal flaring, the score will be 0; if there is intermittent nasal flaring, the score will be 1; and if the nasal flaring is continuous, then the score will be 2.

We evaluated the neonates for 2 times—one before inhalation and the other on the 3rd day of admission using TTN clinical score and respiratory distress score or Down score.

The Down score for respiratory distress consists of the following five items: respiratory rate, retraction, grunting, cyanosis, and air entry.

Respiratory rate: If the respiratory rate is below 60 breaths/min, the score will be 0; if it is 60–80 breaths/min, the score will be 1; and if it is more than 80 breaths/min, then the score will be 2.

Retractions: If there is no retraction, the score will be 0; if there is mild retraction, the score will be 1; and if there is sever retraction, then the score will be 2.

Grunting: If there is no grunting, the score will be 0; if there is grunting which is audible by stethoscope, the score will be 1; and if there is grunting which is audible by the ear, then the score will be 2.

Cyanosis: If there is no cyanosis, the score will be 0; if there is cyanosis relieved by O_2, the score will be 1; and if there is cyanosis with O_2, then the score will be 2.

Air entry: If there is good, equal, bilateral air entry, the score will be 0; if there is a mild decrease in air entry, the score will be 1; and if there is a marked decrease in air entry, then the score will be 2.

STATISTICAL ANALYSIS

All statistical calculations were done on SPSS version 21 (IBM, Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-sample *t*-test was used when comparing two groups in quantitative data. Chi-square (X^2) test was used for comparison between two groups in qualitative data. $P < 0.05$ was considered significant.

RESULTS

This study was conducted on 100 neonates with TTN, which was divided into 2 groups each group consisted of 50 neonates, the 1st group (inhaled steroid group) were exposed to inhalation of corticosteroids and the 2nd group (placebo group) who were exposed to inhalation of placebo. Table 1 shows comparative characteristics between inhaled steroid and placebo groups at birth which reveals that, there was no significant difference between both groups (1st and 2nd groups). The following characteristics were examined in 1st and 2nd groups and revealed that: Weight was 3,857 ± 89.7 and 3,869 ± 91.8 respectively with P = 0.510; gestational age was 39.5 ± 2 and 39.4 ± 2.1 respectively with P = 0.808; APGAR score at 5 min was 8.85 ± 0.65 and 8.9 ± 0.7 respectively with P = 0.712; mode of delivery: cesarean section (CS) was 96% and 94% respectively and NVD were 4% and 6% respectively with P = 0.646; gender: Males were 70% and 72% respectively and female were 30% and 28% respectively with P = 0.826.

Table 2 shows comparative clinical and laboratory evaluation between both groups before

TABLE 1. Comparative Characteristics between Inhaled Steroid and Placebo Groups at Birth

		Inhaled Steroid (1st) group (*N* = 50)		**Placebo (2nd) group (*N* = 50)**		***t*-test**	**P-value**
Weight (kg)	Mean ± SD	3,857 ± 89.7		3,869. ± 91.8		0.663	0.510
Gestational age (weeks)		39.5 ± 2		39.4 ± 2.1		0.239	0.808
APGAR score at 5 min		8.85 ± 0.65		8.9 ± 0.7		0.368	0.712
		N	%	*N*	%	X^2	P-value
Mode of delivery	NVD	2	4	3	6	0.213	0.646
	CS	48	96	47	94		
Sex	Male	35	70	36	72	0.049	0.826
	Female	15	30	14	28		

**Significant if P < 0.05.*

NVD, normal vaginal delivery; CS, cesarean section; APGAR, Activity, Pulse, Grimace, Appearance, Respiration.

TABLE 2. Comparative Clinical and Laboratory Evaluation between Inhaled Steroid and Placebo Groups before Budesonide Inhalation

		Inhaled Steroid Group (*N* = 50)	Placebo Group (*N* = 50)	*t*-test	P-value
Down score	Mean ± SD	5 ± 0.8	5 ± 0.9	0.010	0.998
TTN clinical score		4.2 ± 1.2	4 ± 1.1	0.869	0.387
SpO_2 (%)		96 ± 2.2	96.1 ± 2.3	0.219	0.825
PH		7.28 ± 0.2	7.29 ± 0.3	0.203	0.845

**Significant if P <0.05.*
SpO_2, Saturation of Peripheral Oxygen measured by pulse oximeter; TTN, transient tachypnea of the newborn.

TABLE 3. Comparative Clinical Evaluation between Inhaled Steroid and Placebo Groups on the 3rd Day of Admission (after Budesonide Inhalation)

		Inhaled Steroid Group (*N* = 50)	Placebo Group (*N* = 50)	*t*-test	P-value
Down score	**Mean ± SD**	3 ± 0.7	4.5 ± 1	8.692	0.001*
TTN clinical score		1.8 ± 0.7	2.9 ± 0.9	6.819	0.001*
SpO2(%)		98.2 ± 1	97.4 ± 1.3	3.448	0.008*
PH		7.37 ± 0.3	7.33 ± 0.4	0.573	0.573

**Significant if P < 0.05.*
SpO_2, Saturation of Peripheral Oxygen measured by pulse oximeter; TTN, transient tachypnea of the newborn.

TABLE 4. Number of Babies Who Needed Continuous Positive Airway Pressure (CPAP) and Duration of Hospitalization in Both Groups

	Inhaled Steroid Group (*N* = 50)	Placebo Group (*N* = 50)	*t*-test	P-value
Number of babies who need CPAP	2	6	2.169	0.140
Duration of hospitalization (Mean ± SD)	4.7 ± 0.8	6.2 ± 1.4	6.581	0.001*

**Significant if P < 0.05.*

budesonide inhalation. No significant differences were found between examined groups with respect to Down score, TTN clinical score, SpO2, and PH.

Table 3 shows comparative clinical and laboratory evaluation between both groups on the 3rd day of admission (after budesonide inhalation). Significant differences between both groups were found regarding Down score (P = 0.001), TTN clinical score (P = 0.001), and SpO_2 (P = 0.008), while there was nonsignificant difference between examined groups in respect of PH (P = 0.573). The results showed that the inhaled steroid group was significantly better clinically than the placebo group.

Table 4 shows comparative difference between the neonates who needed CPAP in both groups. No significant difference was found between the examined groups, although the inhaled steroid group was better than the placebo group as there were lower number of neonates who need CPAP compared with the placebo group. and showed comparative difference between the duration of the presence of

the baby in incubator before discharge in both groups which showed significant differences between both groups (P = 0.001) where the inhaled steroid group is significantly better than placebo group as there was significantly lower stay in hospital if compared with placebo group.

DISCUSSION

Transient tachypnea of the newborn is an important cause of chest diseases in neonates, especially in full-term neonates. Although TTN usually has a benign course and may be considered a self-limiting disease, sever patients of TTN may have acute respiratory distress, pneumothorax and persistent hypertension that may need mechanic ventilation.[12]

Cesarean section is a very important risk and predisposing factor for the development of TTN. This may be due to lack of enough time to get rid of fetal alveolar fluid; extra fluid in the respiratory system of neonate during delivery passes from the alveoli to interstitial tissue, leading to airway obstruction and causing respiratory distress.[13]

This study revealed that there was no significant difference in examined neonates regarding weight, gestational age, mode of delivery, gender, and APGAR score. It further revealed that most of the cases of TTN were delivered by cesarean section: 48 cases out of 50 (96%) in inhaled steroid group and 47 cases out of 50 (94%) in the placebo group, and this was in agreement with other studies done for TTN and its relation with cesarean section.[14,15]

The results of this study further revealed that most of the cases of TTN were males: 35 cases out of 50 (70%) in inhaled steroid group and 36 cases out of 50 (72%) in the placebo group, and this was in agreement with other studies which stated that most of the cases of TTN were males. Hence, male gender is demonstrated to be an important risk factor of TTN.[16]

Our study showed that there was a significant difference between the examined neonates in both groups regarding Down score, TTN clinical score, and SpO2 although no difference was found regarding PH; the inhaled steroid group was significantly better clinically than the placebo group.

There was a study whose results are opposite to the results of our study, revealing no beneficial effects on the prognosis and clinical manifestations in neonates with TTN by the administration of inhaled steroids. These disconfirming results could be due to delayed effect of steroid where this point of view was taken in consideration in our study in which we examine the neonate on the day 3 of admission after more than 24 h of inhaled steroid giving time to the inhaled steroid to act on the ENaC of the lung leading to maximum function of these receptors in absorption of the lung fluid.[10]

This study 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 nonsignificant. 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. These results are quite similar to the studies done on neonatal ventilator-associated pneumonia, where the management of this type of pneumonia in neonates with budesonide nebulization decreased the duration of neonatal mechanical ventilation and hospitalization without causing any effect on the future general health and development of patients.[17,18]

Currently, the effectiveness of budesonide in neonatal treatment has been reported frequently from many countries. Some studies have revealed that corticosteroid could normalize lung functions in neonates having inflammatory lung diseases, such as meconium aspiration syndrome, and relieved the alveoli inflammation.[19]

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Some studies have used inhaled procaterol (which is a β2-adrenergic receptor agonist) for treating TTN, although it was not found effective in case of neonates.[20] Other studies have concluded that there was a significant difference between the treatment group and the placebo group regarding treatment duration, duration of hospitalization, and need for CPAP, with beneficial effects of inhaled salbutamol (which is a β2-adrenergic receptor agonist) on the outcomes of neonates with TTN.[21]

Many studies have stated that budesonide could improve pulmonary ventilation in the management of some neonatal respiratory diseases.[17] In our study, budesonide inhalation had led to early improvement in TTN patients, lower number of babies who needed CPAP, and significantly lower hospital stay if compared with the placebo group. This agreed with the studies which stated that timely treatment of neonates having TTN would lead to their protection from the adverse outcomes of long-term incubation, decrease the need for ventilation support and prevent their unnecessary transport to other incubators, all these resulting in good prognosis and better outcomes.[22, 23]

The corticosteroid inhalation intervention is preferred over systemic corticosteroid due to the possible side effects of systemic corticosteroids. Inhaled corticosteroid had proven their efficacy and safety in the treatment of many respiratory diseases, such as bronchial asthma, in infants as well as children.[6]

CONCLUSION

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.

Recommendation

Inhaled budesonide administration in TTN.

Limitation of the study

The limited number of neonates in the study, so more studies should be conducted on the same topic using a larger number of neonates in order to reach an evident conclusion.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

This research was self-funded by the authors.

DATA AVAILABILITY STATEMENT

Parents of all neonates had been signed an informed consent and after taking history from them either the father or grandmother we clarified the nature of the disease and the line of treatment that will be used for their neonates While ensuring the confidentiality of each case.

COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the ethical committee. My research title "Therapeutic effect of inhaled budesonide in transient tachypnea of newborn: A placebo-controlled study" had been reviewed by Thai Clinical Trials Registry (TCTR) Committee. It deemed satisfactory for all items of Trial Registration Data Set required by World Health Organization and had been approved for registration at TCTR. My research TCTR identification number is TCTR20200513005.

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