Efficacy of Budesonide, Epinephrine and Salbutamol Inhalation for Treatment of Transient Tachypnea of Newborn: Prospective Controlled Study

Ahmed M. El-Badawy a, Ashraf M. Ibrahim a, Abd El Rahman M. El-Mashad a and Mostafa M. Awny a

a Pediatrics Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/AJPR/2021/v7i330217
Editor(s):
(1) Dr. Emmanouil Magiorkinis, Athens University Medical School, Greece.
Reviewers:
(1) Patricia Haas, Universidade Federal de Santa Catarina, Brazil.
(2) Gouda Ankula Prasad Kartikeswar, MJM Hospital, India.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/76101

Received 07 September 2021
Accepted 14 November 2021
Published 01 December 2021

ABSTRACT

Background: Transient tachypnea of the newborn (TTN) is a neonatal lung disease which has a picture of lung edema due to delayed resorption of lung fluids. It is commonly seen in full-term or late-preterm infants with an occurrence rate of 5.7 in 1,000 infants. The aim of this work was to compare the efficacy of inhaled budesonide, epinephrine and salbutamol for treatment of TTN.

Methods: This prospective controlled study was conducted on 100 full term neonates with presumed diagnosis of TTN. They were randomly assigned into four groups equally. Group I received nebulized budesonide, Group I received nebulized epinephrine, Group III received nebulized salbutamol and Group IV received nebulized normal saline.

Results: Salbutamol significantly decreased respiratory rate and TTN clinical score, duration of respiratory support along with hospitalization time and helped with reaching full feeding earlier compared to other groups.

Conclusions: Inhaled salbutamol significantly decreased TTN clinical score, shorter duration of respiratory support, hospitalization and earlier initiation of enteral feeding compared to placebo. Inhaled budesonide and epinephrine did not significantly reduce the duration of oxygen treatment, with no other significant effect on TTN.
Keywords: Budesonide; epinephrine; salbutamol; transient tachypnea of newborn.

1. INTRODUCTION

Transient tachypnea of the newborn (TTN) is a neonatal lung disease which has a picture of lung edema due to delayed resorption of lung fluids [1,2]. It is commonly seen in full-term or late-preterm infants with an occurrence rate of 5.7 in 1,000 infants. The disorder is more prevalent among infants who are male, premature, born via cesarean section without labor, or born to a mother with diabetes or asthma, and among infants who have perinatal asphyxia [3,4].

During late gestation, as a result of increased secretion of epinephrine and other hormones, the neonatal mature lung switches from secreting fluid into the air spaces to starting reabsorbing it [5]. Delayed resorption of lung fluid in the fetus is the main cause of TTN where the fluid fills the air spaces and moves into the interstitial tissue, perivascular tissues and interlobar fissures until it is drained by the lymphatics or capillaries [6,7].

Lung liquid clearance at birth is associated with the surge in fetal catecholamines acting via β-adrenergic receptors located in alveolar type II cells and driven by active Na+ absorption by increased epithelial Na+ channels (ENaC) and Na+−K+−ATPase activity [8]. The inability of the fetal lung to switch from fluid secretion to fluid absorption and an immaturity in the expression of the ENaC may play an important role in the development of TTN [9]. Stimulation of β-adrenergic receptors with up-regulates alveolar epithelial Na+ transport by increasing the activity of ENaC and Na+−K+−ATPase and protein abundance at the plasma membrane [9,10].

The importance of catecholamines in improving absorption of fetal lung fluid, it explains why a relative catecholamine deficiency may play a role in the development of TTN. So, administration of exogenous catecholamines may be an effective treatment [11,12]. Levels of circulating catecholamines are higher in newborns delivered vaginally than in newborns delivered by cesarean section may be due to the stimulation of catecholamine release by the stress of labor [13]. Catecholamine levels are lower in infants with TTN than in infants without TTN [14].

Infusion of epinephrine leads to reduction of secretion and promote the absorption of fetal lung fluid [15]. Because TTN is self-limiting and relatively mild symptoms, the risk of systemic epinephrine therapy is not warranted. Inhaled epinephrine, however, is theoretically ideal for reaching the lung while minimizing systemic effects. The only commercially available inhaled epinephrine is racemic epinephrine and it is considered safe [16].

Both animal and human studies suggest lower expression of ENaC subunits, indirectly reflected lower nasal potential differences, as one of possible mechanisms for late preterm and term infants suffering from TTN. Inhaled budesonide was shown to promote transcription of ENaC in lung epithelia as well as reducing the rate of degradation and increasing the activity of the existing channels [17]. This led to clinical trials that explored the role of steroids in preventing TTN. The administration of a single dose of inhaled B2 agonists effectively reduced respiratory morbidity in late preterm and term infants with TTN [18] and glucocorticoids may improve that effect [19].

This study aimed to compare the efficacy of inhaled budesonide, epinephrine and salbutamol for treatment of transient tachypnea of newborns at the neonatal intensive care unit (NICU) of Tanta University hospital.

2. PATIENTS AND METHODS

This prospective controlled study was conducted at neonatal intensive care unit of Tanta University hospital. 100 full term neonates with presumed diagnosis of transient tachypnea of newborn (TTN) were enrolled in this study from December 2018 to June 2020.

The inclusion criteria were full term neonates diagnosed with TTN according to clinical parameters [20] (tachypnea> 60 breaths/minute within 24 hrs after delivery, mild to moderate respiratory distress with nasal flaring and rib retractions [intercostal & subcostal], auscultation reveals good air entry with or without crackles, manifestations usually persist for 12-24 hours. up to 72 hrs and spontaneous improvement is an important marker of TTN), chest x-ray findings [21] (prominent perihilar streakings, fluid in the minor fissure, prominent pulmonary vascular markings, lung hyperinflation with depression of diaphragm and chest x-ray usually shows evidence of clearing by 12-18 hrs with complete
resolution by 48-72 hrs), TTN clinical score to determine the degree of severity [19].

While neonates presented with tachypnea presented within more than 24 hrs. after delivery, severe respiratory distress with cyanosis, congenital heart diseases, evidence of sepsis, inborn error of metabolism, congenital lung malformations and chromosomal disorders were excluded.

The recruited cases were randomly assigned into four groups equally.

Group I (budesonide group) received nebulized budesonide (Pulmicort “0.25 mg/ml” a product of AstraZeneca, Sweden) at dose of 0.5 mg in 2ml 0.9% normal saline every 8 hours till clinical resolution.

Group II (epinephrine group) received nebulized epinephrine (Adrenaline “1 mg/ml” a product of Chemical Industries Development (CID), Egypt) at dose of 0.5 ml/kg of 1:1,000 solution diluted in 2 ml 0.9% normal saline every 8 hours till clinical resolution.

Group III (salbutamol group) received nebulized salbutamol (Farcolin Respirator solution “0.121 gm/20 ml” a product of Pharco, Egypt) at dose of 0.15 ml/kg in 2 ml 0.9% normal saline every 8 hours till clinical resolution.

Group IV (control group) received nebulized normal saline 0.9% at dose of 2 ml 0.9% normal saline every 8 hours till clinical resolution.

2.1 Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.20. Quantitative data were reported as mean±standard deviation (SD). Qualitative data were stated as percentage and frequency. These next tests were held: A one-way analysis of variance (ANOVA) when there is a comparison between over two means with Post Hoc test: Least Significant Difference (LSD) was utilized for numerous comparisons between different variables. Chi-square (x^2) significance test was utilized for comparing proportions among qualitative parameters. The confidence interval was set to 95% and the error margin accepted was set to 5%. P-value ≤0.05 was considered significant.

3. RESULTS

In Table 1 there were no significant differences among studied groups at time of enrollment as regards to sex, age, gestational age, birth weight or Apgar score at 1, 5 minutes as (p > 0.05). It also showed that 82% of the neonates were delivered via Caesarian section while 18% were delivered by normal vaginal delivery. As regards to mother common morbidities, 10% had hypertension, 11% had diabetes mellitus and 5% had bronchial asthma, so there was predominance of Caesarian section as risk factor.

In Table 2 there was insignificant difference among groups as p > 0.05 as regards grade of respiratory distress. Most cases 64% were manifested with tachypnea, 25% were manifested with retractions and 11% were manifested with grunting.

As regards to the method of respiratory support, there was insignificant difference among groups as p > 0.05. Most cases 62% received LFNC as supplemental O2 at time of enrollment, 20% of cases received incubator O2 and 18% of cases received CPAP.

In Table 3 and Table 4 there was insignificant difference in heart rate at time of enrollment and after 48 hrs among the studied groups as p > 0.05. As regards respiratory rate, there was no statistically significant difference at time of enrollment. After 48 hrs there was decrease in both budesonide and epinephrine groups but was statistically insignificant versus control group as p > 0.05. The decrease was more in salbutamol group with statistically significant difference versus other groups as p < 0.05.

In Table 5 at time of enrollment there was no statistically significant difference among groups, but after 48 hrs there were statistically significant differences among them. There was decrease in both budesonide and epinephrine groups but was statistically insignificant versus control group as p > 0.05. The decrease was more in salbutamol group with statistically significant difference versus other groups as p < 0.05.

Table 6 showed that PH, PaO2 and HCO3 increased after treatment, while PCO2 decreased, but there was insignificant difference among groups as P > 0.05.
### Table 1. Demographic data and maternal characteristics of the studied groups

|                  | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|------------------|------------------------|-------------------------|------------------------|---------------------|---------|
| **Sex**          |                        |                         |                        |                     |         |
| Male             | 14 (56.0 %)            | 14 (56.0 %)             | 16 (64.0 %)            | 17 (68.0 %)         | 0.769   |
| Female           | 11 (44.0 %)            | 11 (44.0 %)             | 9 (36.0 %)             | 8 (32.0 %)          |         |
| **Age at enrollment (hours)** | 3.88 ±3.55 | 4.44 ± 1.08 | 5.88 ±4.48 | 5.36 ±3.20 | 0.168 |
| **Gestational age (Weeks)** | 37.68 ± 0.99 | 38.08 ± 1.04 | 37.48 ± 0.65 | 37.68 ± 0.99 | 0.146 |
| **Birth weight (Kg)** | 3.66 ± 0.74 | 3.69 ± 0.58 | 3.62 ± 0.60 | 3.55 ± 0.67 | 0.896 |
| **Apgar score 1min** | 7.40 ± 0.50 | 7.32 ± 0.48 | 7.60 ± 0.50 | 7.40 ± 0.50 | 0.230 |
| **Apgar score 5 min** | 9.0 ± 0.0 | 9.0 ± 0.0 | 8.92 ± 0.28 | 8.88 ± 0.33 | 0.130 |
| **Mode of delivery** | CS | 20 (80 %) | 21 (84 %) | 19 (76 %) | 22 (88 %) | 0.816 |
|                  | Vaginal | 5 (20%) | 4 (16%) | 6 (24%) | 3 (12%) |         |
| **Maternal characteristics** | Maternal hypertension | 3 (12%) | 2 (8%) | 1 (4%) | 4 (16%) | 0.682 |
|                  | Maternal asthma | 1 (4%) | 2 (8%) | 0 (0%) | 2 (8%) | 0.752 |
|                  | Maternal diabetes | 2 (8%) | 2 (8%) | 3 (12%) | 4 (16%) | 0.895 |
|                  | Maternal age (years) | 31.8 ±4.9 | 32.7 ±5.9 | 31.7 ±5.4 | 30.6 ± 4.5 | 0.564 |

**CS**: Cesarean section.

### Table 2. Grades and methods of support of respiratory distress in the studied groups

| Grade of RD   | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|---------------|------------------------|-------------------------|------------------------|---------------------|---------|
| RD I (tachypnea) | 17                      | 68.0                    | 16                      | 64.0                | 15      | 60.0    | 0.985 |
| RD II (retractions) | 6                      | 24.0                    | 6                       | 24.0                | 7       | 28.0    | 6.240 |
| RD III (grunting) | 2                      | 8.0                     | 3                       | 12.0                | 2       | 8.0     | 4.160 |
| RD IV (cyanosis) | 0                      | 0                       | 0                       | 0                   | 0       | 0       | 0.000 |
| **Methods of support** | CPAP | 5                       | 20.0                    | 3                     | 12.0                | 4       | 16.0    | 6      | 24.0    | 0.910 |
|                  | LFNC | 14                      | 56                      | 18                    | 72                  | 16      | 64      | 14      | 56      |         |
|                  | Incubator O2 | 6                      | 24.0                    | 4                     | 16.0                | 5       | 20.0    | 5       | 20.0    |         |

**RD**: respiratory distress, MC: Monte Carlo, **CPAP**: continuous positive airway pressure, **LFNC**: low flow nasal cannula.
Table 3. Heart and respiratory rate at enrollment (0), 12, 24, 48 hrs of the studied groups

| Time                          | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|-------------------------------|------------------------|-------------------------|------------------------|---------------------|---------|
| 0 h (at enrollment) (b/m)     | 125.96 ± 7.21          | 124.32 ± 7.40           | 123.0 ± 6.26           | 128.36 ± 7.30       | 0.051   |
| 12 h (b/m)                   | 136.60 ± 5.93          | 136.24 ± 6.22           | 138.64 ± 3.43          | 133.64 ± 6.95       | 0.029   |
| 24 h (b/m)                   | 129.48 ± 6.11          | 130.84 ± 6.20           | 128.36 ± 6.74          | 128.12 ± 7.80       | 0.470   |
| 48 h (b/m)                   | 125.44 ± 5.27          | 127.40 ± 5.85           | 123.28 ± 5.0           | 124.32 ± 7.66       | 0.101   |

Respiratory rate

| Time                          | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|-------------------------------|------------------------|-------------------------|------------------------|---------------------|---------|
| 0 h (at enrollment) (cycle/min) | 72.56 ± 4.74          | 72.96 ± 5.26           | 72.92 ± 5.11           | 73.56 ± 4.64       | 0.912   |
| 12 h (cycle/min)             | 60.64 ± 4.84          | 60.76 ± 5.55           | 58.40 ± 5.21           | 61.48 ± 4.42       | 0.160   |
| 24 h (cycle/min)             | 50.88 ± 3.89          | 51.60 ± 4.69           | 46.60 ± 4.78           | 52.24 ± 4.36       | <0.001  |
| 48 h (cycle/min)             | 45.48 ± 5.11          | 46.24 ± 5.39           | 41.88 ± 4.70           | 48.0 ± 3.14        | <0.001  |

h: hour, statistically significant p value: ≤ 0.05

Table 4. Respiratory rate changes of the studied groups

| Time                          | G1 Control vs. G2 Control | G1 Control vs. G3 Control | G1 Control vs. G2 | G1 Control vs. G3 | G2 Control vs. G3 |
|-------------------------------|----------------------------|----------------------------|-------------------|-------------------|-------------------|
| At enrollment (0 H)           | 0.891                      | 0.973                      | 0.968             | 0.992             | 0.994             | 1.000             |
| After 48 H                    | 0.231                      | 0.544                      | <0.001            | 0.939             | 0.037             | 0.007             |

H (hour), statistically significant p value: ≤ 0.05, G1: Budesonide G 2: Epinephrine G 3: Salbutamol G 4: normal saline.

Table 5. TTN clinical score changes at enrollment (0), 12, 24, 48 hrs of the studied groups

| Time                          | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|-------------------------------|------------------------|-------------------------|------------------------|---------------------|---------|
| 0 h (at enrollment)           | 2.64 ± 0.70            | 2.76 ± 0.83             | 2.52 ± 0.71            | 2.92 ± 1.04         | 0.445   |
| 12 h                          | 1.68 ± 0.69            | 1.76 ± 0.78             | 1.68 ± 0.69            | 2.08 ± 0.70         | 0.114   |
| 24 h                          | 0.92 ± 0.64            | 0.96 ± 0.68             | 0.36 ± 0.57            | 1.20 ± 0.50         | <0.001  |
| 48 h                          | 0.32 ± 0.48            | 0.36 ± 0.49             | 0.04 ± 0.20            | 0.40 ± 0.50         | 0.020   |

TTN clinical score changes

| Time                          | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P value |
|-------------------------------|------------------------|-------------------------|------------------------|---------------------|---------|
| At enrollment (0 H)           | 0.131                  | 0.154                   | 0.79                   | 0.689               | 0.505   | 0.286   |
| After 48 H                    | 0.531                  | 0.754                   | 0.005                  | 0.754               | 0.028   | 0.012   |

H (hour), TTN: transient tachypnea of newborn, pairwise comparison bet. each 2 groups were done using Post Hoc test (Dunn's for multiple comparisons test), Statistically significant at p ≤ 0.05, G1: Budesonide G 2: Epinephrine G 3: Salbutamol G 4: normal saline.
### Table 6. Capillary blood gases of the studied groups

|                     | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P     |
|---------------------|------------------------|-------------------------|------------------------|--------------------|-------|
| **PH:**             |                        |                         |                        |                    |       |
| Before treatment    | 7.29 ± 1.2             | 7.31 ± 0.88             | 7.30 ± 1.0             | 7.30 ± 0.6         | 1.000 |
| After treatment     | 7.36 ± 0.92            | 7.44 ± 0.53             | 7.42 ± 0.6             | 7.35 ± 0.85        | 0.936 |
| **PaCO2:** (mmHg)   |                        |                         |                        |                    |       |
| Before treatment    | 50.52 ± 9.23           | 47.85 ± 7.64            | 49.32 ± 8.15           | 53.22 ± 10.34      | 0.185 |
| After treatment     | 45.91 ± 6.89           | 44.33 ± 5.32            | 44.35 ± 6.12           | 44.15 ± 7.12       | 0.756 |
| **PaO2:** (mmHg)    |                        |                         |                        |                    |       |
| Before treatment    | 53.13 ±10.23           | 56.1 ± 8.99             | 55.2 ± 8.20            | 56.2 ± 8.99        | 0.612 |
| After treatment     | 72.39 ± 8.12           | 73.22 ± 6.12            | 72.2 ± 5.77            | 71.4 ± 6.32        | 0.463 |
| **HCO3:** (mmol/l)  |                        |                         |                        |                    |       |
| Before treatment    | 20.33 ± 6.45           | 22.35 ± 5.44            | 20.12 ± 6.32           | 21.33 ± 6.01       | 0.377 |
| After treatment     | 22.35 ± 5.15           | 23.45 ± 4.32            | 23.48 ± 4.22           | 23.53 ± 4.19       | 0.425 |

### Table 7. O₂ saturation at enrollment (0), 12, 24, 48 hrs of the studied groups

|                     | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P     |
|---------------------|------------------------|-------------------------|------------------------|--------------------|-------|
| 0 h (at enrollment) (%) | 90.52 ± 1.05           | 90.20 ± 1.47            | 90.24 ± 1.20           | 89.84 ± 1.31       | 0.310 |
| 12 h (%)            | 94.04 ± 1.37           | 94.28 ± 1.62            | 93.52 ± 1.76           | 93.44 ± 1.29       | 0.156 |
| 24 h (%)            | 95.80 ± 1.08           | 95.64 ± 1.22            | 95.08 ± 1.71           | 95.08 ± 0.95       | 0.096 |
| 48 h (%)            | 95.88 ± 2.20           | 95.56 ± 1.08            | 95.72 ± 2.69           | 94.72 ± 1.10       | 0.144 |

*H: hour*

### Table 8. Duration of respiratory support and duration of hospitalization of the studied groups

|                     | G1 Budesonide (n = 25) | G2 Epinephrine (n = 25) | G3 Salbutamol (n = 25) | G4 Control (n = 25) | P     |
|---------------------|------------------------|-------------------------|------------------------|--------------------|-------|
| **Duration of**     |                        |                         |                        |                    |       |
| **respiratory**     |                        |                         |                        |                    |       |
| **support** (hours) | Mean ± SD.             |                         |                        |                    |       |
|                    | 32.75 ± 13.20          | 30.32 ± 10.39           | 21.52 ± 8.17           | 38.12 ± 14.32      | <0.001|
| **Duration of**     |                        |                         |                        |                    |       |
| **hospitalization** | Mean ± SD.             |                         |                        |                    |       |
|                    | 2.42 ± 0.48            | 2.36 ± 0.40             | 2.0 ± 0.38             | 2.56 ± 0.46        | <0.001|

*Statistically significant at p ≤ 0.05*
In late gestation and shortly before birth, fetal absorption is relatively low. Alveolar fluid which in turn modulates lung growth. Na alveolar epithelium actively secretes cl into secreted by the lung epithelium. Pulmonary In utero the lungs are filled with a liquid that is resorption of the fetal lung fluid, which fills the early respiratory distress because of delayed newborn (TTN) is the most frequent cause of Our study showed insignificant differences among groups as regards grades of respiratory distress at time of enrollment. That was in agreement with [24]. There were insignificant differences among groups as regards methods of respiratory support as p > 0.05. That was in agreement with [25]. As regards to heart rate, the current study showed that there were insignificant differences before and after inhalation and that was in agreement with [26, 27]. In this study, at time of enrollment, mean respiratory rate and mean of TTN score were relatively higher. However, after 48 hours there was a noticeable decrease in budesonide, epinephrine, and salbutamol groups. As regards to respiratory rate and TTN clinical score after 48 hrs, the comparison of budesonide and epinephrine to control group showed insignificant differences as p > 0.05 and that was in agreement with [28] and [29] respectively. The decrease was significant in salbutamol group in comparison to other groups. That was in agreement with [30] as both respiratory rate and TTN score significantly decreased in salbutamol group (treatment group) when compared to normal saline group (control group) at half hour after treatment and continued till 8 hours after treatment.

In Table 7, as regards O₂ saturation there was insignificant difference at enrollment and after 48 hrs among all groups as P > 0.05.

In Table 8, as regards the duration of respiratory support and the duration of hospitalization after 48 hrs there were insignificant differences between budesonide and epinephrine groups versus control group as p > 0.05. The both durations were less in salbutamol group but were statistically significant versus other groups as p <0.05.

In Fig. (1), as regards time till full feeding, there was statistically significant difference among groups asp <0.05, but when comparing budesonide and epinephrine groups versus control group, there was no statistically difference as p > 0.05. Salbutamol group reached full feeding earlier with significant difference versus other groups as p <0.05.

4. DISCUSSION

In the neonatal period, transient tachypnea of the newborn (TTN) is the most frequent cause of early respiratory distress because of delayed resorption of the fetal lung fluid, which fills the fetal airways [22]. In utero the lungs are filled with a liquid that is secreted by the lung epithelium. Pulmonary alveolar epithelium actively secretes cl into developing air space, promoting fluid secretion, which in turn modulates lung growth. Na absorption is relatively low. Alveolar fluid continuously passes to amniotic fluid by breathing movements via broncho-tracheal route. In late gestation and shortly before birth, fetal lungs convert from fluid secretion to fluid re-

In this study, Fig. (1) shows the Time till full feeding in hours of the studied and control groups.
Regarding capillary blood gases before and after nebulization, there were insignificant differences between groups in pH, PaO$_2$, PaCO$_2$ and HCO$_3$ and that was in disagreement with [26] and [24,26]. In [26], the studied neonates were divided into three groups: group 1 received one dose of inhaled epinephrine, group 2 received one dose of inhaled salbutamol and group 3 (control group) received saline 0.45% and there were significant differences between groups in pH, PaO$_2$, PaCO$_2$ after nebulization. Saline group recorded the lowest readings of pH and PaO$_2$ in comparison to the other groups, but the highest reading in PaCO$_2$. In salbutamol group, there was significant increase in PH, PaO$_2$ and significant decrease in PaCO$_2$ after nebulization.

In our study as regards O$_2$ saturation, there were insignificant differences at enrollment and after 48 hrs as p > 0.05 and that was not in agreement with [25] where there was significant difference between salbutamol and control groups after 4 hours.

As regards the duration of respiratory support and the duration of hospitalization, all were shorter than control group. They were significantly shorter with salbutamol group than other groups and that was in agreement with [27] which investigated 100 neonates with TTN to receive nebulized normal saline solution or salbutamol in saline solution. This study reported that the duration of respiratory support and duration of hospitalization were significantly shorter in salbutamol group than control group.

While the comparison of budesonide and epinephrine to control group showed insignificant differences as p > 0.05 and that was in in agreement with [28] and [29].

The mean time till full feeding in hours in budesonide group was shorter than in control group, but salbutamol group reached full feeding earlier with significant differences in comparison to other groups and that was in agreement with [31], where neonates were assigned to receive either salbutamol inhalation or normal saline inhalation as placebo group, where salbutamol group reached full feeding earlier with significant differences.

Also, budesonide and epinephrine reached full feeding earlier than control group, but with insignificant differences and that was in agreement with [28,29].

5. CONCLUSIONS

Inhaled salbutamol significantly decreased TTN clinical score, shorter duration of respiratory support, hospitalization and earlier initiation of enteral feeding compared to placebo. Inhaled budesonide and epinephrine did not significantly reduce the duration of oxygen treatment, with no other significant effect on TTN.

6. STRENGTHS AND LIMITATIONS

One of the strengths of the present study was its prospective controlled approach which facilitated investigating and examining the hypothesis of the researcher.

On the other hand, the main limitations of the study was the small sample size and the time limit required for completion of our investigation.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The study was approved by Ethics Committee of Faculty of Medicine, Tanta University. Written informed consent was obtained from the guardians of every patient.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Avery ME, Gatewood OB, Brumley G. Transient tachypnea of newborn. Possible delayed resorption of fluid at birth. Am J Dis Child. 1966;111:380-5.
2. Katz C, Bentur L, Elias N. Clinical implication of lung fluid balance in the perinatal period. J Perinatol. 2011;31:230-5.
3. Lewis V, Whitelaw A. Furosemide for transient tachypnea of the newborn. Cochrane Database Syst Rev. 2002;Cd003064.
4. Takaya A, Igarashi M, Nakajima M, Miyake H, Shima Y, Suzuki S. Risk factors for transient tachypnea of the newborn in infants delivered vaginally at 37 weeks or later. J Nippon Med Sch. 2008;75:269-73.
5. Liu J, Chen XX, Li XW, Chen SW, Wang Y, Fu W. Lung ultrasonography to diagnose transient tachypnea of the newborn. Chest. 2016;149:1269-75.
6. Kassab M, Khriesat WM, Anabrees J. Diuretics for transient tachypnoea of the newborn. Cochrane Database Syst Rev. 2015;2015:Cd003064.
7. Stroustrup A, Trasande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. J Pediatr. 2012;160:38-43.e1.
8. Barker PM, Olver RE. Invited review: Clearance of lung liquid during the perinatal period. J Appl Physiol (1985). 2002;93:1542-8.
9. Davies JC. Ion transport in lung disease. Pediatr Pulmonol Suppl. 2004;26:147-8.
10. Mutlu GM, Factor P. Alveolar epithelial beta2-adrenergic receptors. Am J Respir Cell Mol Biol. 2008;38:127-34.
11. Frank JA, Wang Y, Osorio O, Matthay MA. Beta-adrenergic agonist therapy accelerates the resolution of hydrostatic pulmonary edema in sheep and rats. J Appl Physiol (1985). 2000;89:1255-65.
12. Sakuma T, Folkesson HG, Suzuki S, Okaniwa G, Fujimura S, Matthay MA. Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med. 1997;155:506-12.
13. Gugliani L, Lakshminrusimha S, Ryan RM. Transient tachypnea of the newborn. Pediatr Rev. 2008;29:e59-65.
14. Brown MJ, Olver RE, Ramsden CA, Strang LB, Walters DV. Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. J Physiol. 1983;344:137-52.
15. Lawson EE, Brown ER, Torday JS, Madansky DL, Taesch HW, Jr. The effect of epinephrine on tracheal fluid flow and surfactant efflux in fetal sheep. Am Rev Respir Dis. 1970;118:1023-6.
16. Kao B, Stewart de Ramirez SA, Belfort MB, Hansen A. Inhaled epinephrine for the treatment of transient tachypnea of the newborn. Journal of Perinatology. 2008;28:205-10.
17. Venkatesh VC, Katzberg HD. Glucocorticoid regulation of epithelial sodium channel genes in human fetal lung. Am J Physiol. 1997;273:L227-33.
18. Jobe AH, Ikegami M, Padbury J, Polk DH, Koririmili A, Gonzales LW, et al. Combined effects of fetal beta agonist stimulation and glucocorticoids on lung function of preterm lambs. Biol Neonate. 1997;72:305-13.
19. Armangil D, Yurdakök M, Korkmaz A, Yiğit S, Tekinalp G. Inhaled beta-2 agonist salbutamol for the treatment of transient tachypnea of the newborn. J Pediatr. 2011;159:398-403.e1.
20. Raimondi F, Yousef N, Rodriguez Fanjul J, De Luca D, Corsini I, Shankar-Aguilera S, et al. A multicenter lung ultrasound study on transient tachypnea of the neonate. Neonatology. 2019;115:263-8.
21. Jain L, Eaton DC. Alveolar fluid transport: A changing paradigm. Am J Physiol Lung Cell Mol Physiol. 2006;290:L646-8.
22. Keleş E, Gebeşçe A, Demirdöven M, Yazgan H, Baştürk B, Tonbul A. The effects of inhaled β-adrenergic agonists in transient tachypnea of the newborn. Glob Pediatr Health. 2016;3:2333794x16645258.
23. van Vonderen JJ, Roest AA, Walther FJ, Blom NA, van Lith JM, Hooper SB, et al. The influence of crying on the ductus arteriosus shunt and left ventricular output at birth. Neonatology. 2015;107:108-12.
24. Malakan A, Dehdashilian M, Aramesh MR, Aletayeb MH, Heidari S. The effect of inhaled salbutamol on the outcomes of transient tachypnea of the newborn. J Chin Med Assoc. 2018;81:990-7.
25. Babaee H, Dabiri S, Mohammadi Pirkashani L, Mohsenpour H. Effects of salbutamol on the treatment of transient tachypnea of the newborn. Iranian Journal of Neonatology JIN. 2019;10:42-9.
26. Nawar F, Aly H, Helmy S, El Monaem M. Is salbutamol and adrenalin inhalation effective in management of transient tachypnia of newborn? J adv med med res. 2016;14:1-8.
27. Talaat AA, Abohashish MMA, Farid TM, Salah MM. Evaluation of inhaled beta-2 agonist in management of transient tachypnea of the newborn. Bulletin of the National Research Centre. 2020;44:12.
28. Vaisbourd Y, Abu-Raya B, Zangen S, Arnon S, Riskin A, Shoris I, et al. Inhaled corticosteroids in transient tachypnea of the newborn: A randomized, placebo-controlled study. Pediatr Pulmonol. 2017; 52:1043-50.

29. Moresco L, Calevo MG, Baldi F, Cohen A, Bruschettini M. Epinephrine for transient tachypnea of the newborn. Cochrane Database Syst Rev. 2016; Cd011877.

30. Salama AA, El-Seheimy LA-F, Elsamanoudy MI. Inhaled Salbutamol for the Treatment of transient tachypnea of the newborn. International Journal of Medical Arts. 2020;2:457-61.

31. Mohammadzadeh I, Akbarian-Rad Z, Heidari F, Zahedpasha Y, Haghshenas-Mojaveri M. The effect of inhaled salbutamol in transient of tachypnea of the newborn: A randomized clinical trial. Iran J Pediatr. 2017;27:e9633.