



Is Salbutamol and Adrenalin Inhalation Effective in Management of Transient Tachypnea of Newborn?

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FN and HAA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author SH managed the literature searches and analyses of the study performed the spectroscopy analysis. Author MAEM managed the experimental process. Author HAA identified the species of plant. All authors read and approved the final manuscript.

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ABSTRACT

Background: In the neonatal period, transient tachypnea of the newborn (TTN) is the most frequent cause of early respiratory distress because of delayed resorption of lung fluid, which fills the fetal airways. The inability of the lung to switch from fluid secretion to fluid absorption and immaturity in the expression of epithelial Na⁺- channels (ENaC) may play an important role in the development of transient tachypnea of the newborn.

Aims: Evaluation of inhalation therapy by BETA-2 agonist salbutamol and epinephrine for the management of transient tachypnea of newborn.

Methods: The study was a prospective randomized control study. It included 60 neonates diagnosed clinically and radiologically as TTN. Inhaled salbutamol, epinephrine or saline 0.45% solution was administered.

Results: Comparing studied groups after intervention, highly significant lower respiratory rate, TTN scores, respiratory support and duration of hospital stay was detected in group II (salbutamol group) while no significant difference between groups regarding heart rate after 4 hours from intervention.

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Conclusion: Inhaled Salbutamol resulted in better outcome in decreasing the respiratory rate, TTN clinical score, lower FIO₂, higher O₂ saturation, decreasing the duration of respiratory support along with the total duration of hospitalization.

Keywords: Salbutamol; adrenalin; transient tachypnea; newborn.

1. INTRODUCTION

Postnatal respiratory complications among term infants are common. The most commonly reported cause of neonatal respiratory distress in late preterm is transient tachypnea of the newborn [1].

The disorder is reported to be benign and self-limiting, with resolution usually occurring by 2 to 5 days of age. In uncommon severe courses of transient tachypnea of the newborn, complications such as pneumothorax need for extracorporeal membrane oxygenation, and death have been reported [2].

There are increasing data to suggest that transient tachypnea of the newborn increases a newborn's risk for developing a wheezing syndrome early in life [3]. Throughout gestation, the presence of an adequate amount of lung fluid is critical for normal lung growth and for the development of the fetal lung to complete transition from intrauterine to extra uterine life [4]. Most interstitial lung liquid moves into the pulmonary circulation and some drains via the lung lymphatic vessels [5]. Transient tachypnea of the newborn is believed to result from delayed resorption of fluid from the lungs of the newborn, which is an important diagnostic and therapeutic dilemma in the NICU [6]. 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 sodium (Na⁺) absorption by increased epithelial Na⁺-channels (ENaC) and sodium-potassium adenosinetriphosphatase (Na⁺-K⁺-ATPase) activity [7].

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 [8].

Both experimental and limited clinical data in adult patients suggest that inhaled or intravenous beta adrenergic agonists accelerate clearance of excess fluid from the alveolar airspace, creating the possibility of their use for treatment of pulmonary edema and acute lung injury [9].

To prevent the systemic side effects of beta agonists, aerosolized beta agonists have been used in the therapy of transient tachypnea of the newborn [10].

Evaluation of inhalation therapy by BETA-2 agonist salbutamol and epinephrine for the management of transient tachypnea of newborn.

2. PATIENTS AND METHODS

2.1 Patients

The study was a prospective randomized control study. It included 60 neonates (35 males and 25 females) diagnosed clinically and radiologically as TTN, who was selected from NICU of Sayed Galal University Hospital between June 2013 and June 2014. The study was approved by the Institutional Ethical Committee.

The studied neonates were divided into three groups randomly:

Group 1: It included 20 neonates with gestational age >35 weeks and postnatal age <6 hours old, diagnosed clinically and radiologically as TTN and received one dose of inhaled epinephrine (the dose is 0.05 ml/kg). The drug was nebulized with 100% oxygen.

Group 2: It included 20 neonates with gestational age >35 weeks and postnatal age <6 hours old, diagnosed clinically and radiologically as TTN and received one dose of inhaled salbutamol (the dose is 0.15 mg/kg). The drug was nebulized with 100% oxygen.

Group 3: It included 20 neonates with gestational age >35 weeks, postnatal age <6 hours old and Downs' score >4, diagnosed clinically and radiologically as TTN as a control group they inhaled saline 0.45%.

Written informed consents were obtained from all the parents of the study patients.

Chest radiograph indicating at least one of the following: Prominent central vascular marking, Widened interlobar fissures of pleural fluid Symmetrical perihilar congestion and Hyperaeration as evidenced by flattening and

depression of the diaphragmatic domes or increased anteroposterior diameter or both.

The excluded neonates were one of the following: Gestational age <35 weeks, Respiratory distress syndrome, Sepsis and pneumonia, Meconium aspiration, Congenital cardiac diseases, Perinatal asphyxia, Congenital lung malformation, Non respiratory causes of respiratory distress (hypocalcaemia, metabolic acidosis, persistent hypoglycemia and polycythemia), Persistent pulmonary hypertension of the newborn and Newborn with ventilation support or arrhythmia.

2.2 Methods

All patients in the study were subjected to:

2.2.1 Complete history taking: With special emphasis on

- **Antenatal history:** Maternal diseases (asthma, diabetes mellitus and others), maternal drugs (aspirin, salbutamol, heparin, cytotoxic drugs), maternal infection (STORCH infection), premature rupture of membranes.
- **Natal history:** Gestational age, neonatal sex and mode of delivery.

2.2.2 Clinical examination

- Gestational age assessment, weight in kilograms, sex (male or female), Assessment of gestational age, (before inhalation therapy) by new Ballard score.
- Complete examination including cardiac, chest, abdominal, and neurological examination (before inhalation therapy).
- **Down's** Score for evaluation of respiratory distress before inhalation therapy and after inhalation therapy at 30 minutes, 1 hour and 4 hours.
- Heart rate (before inhalation therapy and after inhalation therapy at 30 minutes, 1 hour and 4 hours.).
- Respiratory rate (before inhalation therapy and after inhalation therapy at 30 minutes, 1 hour and 4 hours.).
- Duration of respiratory support (in hours), and duration of hospitalization (in days).

2.2.3 Investigation

2.2.3.1 Laboratory investigation

- **Capillary blood gases:** (before and after inhalation therapy):

- pH, PaO₂, and PaCO₂ was measured.
- **FiO₂ (%):** (at the time of diagnosis, after 0.5 an hour, after 1 hour, after 4 hours). FiO₂ (fraction of inspired oxygen) and level of respiratory support are measured as follow: FiO₂ = (Flow Rate(in LPM) x 4) +21%
- **O₂ saturation:** At the time of diagnoses, after 0.5 an hour, after 1 hour, after 4 hours. Heart rate and oxygen saturation were assisted by pulse oxymeter.

2.2.3.2 Chest X-ray

Chest X-ray was done initially before intervention to confirm the diagnosis.

2.3 Statistical Method

Results on continuous measurements are presented as Mean + SD. Data obtained were analyzed by one way analysis of variance through graphpadinstat program.

3. RESULTS

3.1 Demographic Data

In this study, 60 neonates diagnosed clinically and radiologically as TTN were divided into three groups randomly as Group I (inhaled Epinephrine), Group II (inhaled Salbutamol) and Group III (inhaled saline) for the management of transient tachypnea of newborn.

There was no statistical significant difference between groups in sex distribution or birth weight or gestational age. *There was also no significant difference between groups in mean readings of APGAR score (Table 1).*

3.2 pH and Blood Gases

There were significant differences ($p < 0.001$) between groups in pH, PaO₂, PaCO₂ after nebulization. Saline group recorded the lowest readings of pH and PaO₂ in comparison to the other groups, but the highest reading in PaCO₂. In salbutamol group: there was significant increase ($p < 0.001$) in PH, PaO₂ and significant decrease ($p < 0.001$) in PaCO₂ after nebulization. On the other hand, the difference between after and before exhibited a significant difference in group I and II for pH (see Table 2).

3.3 Oxygen Saturation and FiO₂

There was significant difference ($p < 0.001$) between groups in O₂ after 1 & 4 hours.

Adrenaline group recorded the lowest readings in comparison to the other groups. There was significant difference ($p < 0.001$) between groups in FiO_2 after 4 hours, salbutamol group recorded the least readings in comparison to the other groups. For SpO_2 , difference between after and before recorded a significant difference in group II ($p < 0.001$). Also, the same result for FiO_2 was recorded (for more details see Table 3).

3.4 Heart Rate and Respiratory Rate

There was significant difference between groups in heart rate before and after nebulization. Adrenaline group recorded the highest readings in comparison to the other groups after nebulization. There was significant difference between groups in respiratory rate after 1 ($p < 0.01$) & 4 ($p < 0.001$) hours, salbutamol group recorded the least readings in comparison to the

other groups. In salbutamol group: there was no significant change in heart rate but significant decrease ($p < 0.001$) in respiratory rate 4 hours after nebulization in comparison to base line readings. No significant difference was recorded for HR in the difference between after 4h and before. However, a significant difference ($p < 0.001$) was recorded in RR group II for the difference between after 4h and before (for more details see Table 4).

3.5 Downes' Score

There was a significant difference ($p < 0.001$) between groups in *Downes'* score after 1 & 4 hours, salbutamol group recorded the least readings in comparison to the other groups. On the other hand, a significant difference ($p < 0.0001$) was exhibited in group II for the difference in *Downes'* scores before and after 4h (see Table 5).

Table 1. Demographic data for the studied groups

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	Test of significance	P value
Sex					
Females	9 (45%)	7 (35%)	9 (45%)	X ² =0.55	0.760
Males	11 (55%)	13 (65%)	11 (55%)		
Birth weight (kg)					
Mean ± SD	3.28±0.45	3.3 ±0.45	3.21±0.51	F=0.19	0.824
Gestational age (weeks)					
Mean ± SD	37.6±1.19	37.75±1.25	38±1.38	F=0.50	0.607
Birth weight/gestational age					
AGA	17 (85%)	17 (85%)	16 (80%)	X ² =0.54	0.969
LGA	2 (10%)	2 (10%)	2 (10%)		
SGA	1 (5%)	1 (5%)	2 (10%)		
APGAR score 5minutes					
Mean ± SD	7.85±0.75	7.95±0.69	7.60±0.68	F=1.31	0.278

AGA: Appropriate for gestational age, LGA: Large for gestational age. SGA: Small for gestational age

Table 2. pH and blood gases (Mean ± SD) before and after nebulization

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	F	P value
pH before nebulization	7.29±0.03	7.29±0.03	7.29±0.02	0.24	0.790
pH after 4 hours	7.30±0.03	7.38±0.02	7.29±0.03		
Difference between after & before	P=0.055	P=0.001	P=0.762		
PaO ₂ before nebulization	51.6±8.75	51.55±8.77	49.65±6.34	0.38	0.684
PaO ₂ after 4 hours	52.3±7.49	57.85±2.32	48.4±5.04		
Difference between after & before	P=0.163	P=0.003	P=0.087		
PaCO ₂ before nebulization	47.85±7.64	47.1±8.4	51.1±7.43	1.47	0.238
PaCO ₂ after 4 hours	48.8±5.64	43±2.59	53±7.03		
Difference between after & before	P=0.140	P=0.032	P=0.071		

Table 3. Oxygen saturation and FiO₂ (Mean ± SD) before and after nebulization

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	F	P value
SpO ₂ before nebulization	89.35±1.14	88.85±1.73	89.9±1.27	2.7	0.07
SpO ₂ after 1/2 hour	89.6±1.05	90.1±1.41	89.4± 1.27	1.65	0.200
SpO ₂ after 1 hr	89.9±0.72	91.35±1.42	90.65±1.27	7.59	0.001
SpO ₂ after 4 hours	90.2±1.16	93.75±1.29	90.7±1.53	41.1	0.001
Difference between after 4 hr & before	P=0.06	P=0.001	P=0.07		
FiO ₂ before nebulization	49.5±10.48	49.65±10.43	48.6±4.22	0.08	0.922
FiO ₂ after 1/2 hour	48.7±10.32	46.55±10.35	48.55±4.19	0.37	0.690
FiO ₂ after 1 hr	48±10.56	43.35±10.16	46.95±4.65	1.51	0.230
FiO ₂ after 4 hours	47.2±10.14	27.85±6.71	46.3±5.48	40.23	0.001
Difference between after 4hr & before	P=0.48	P=0.001	P=0.14		

FiO₂: Fraction of inspired oxygen

Table 4. Heart rate and respiratory rate (Mean ± SD) before and after nebulization

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	F	P value
HR before nebulization	139.9±5.11	137.9±5.11	141.7±5.4	2.58	0.08
HR after 1/2 hour	165.5±6.71	137.75±4.94	140.4±2.87	181.19	0.001
HR after 1 hr	165.15±6.46	137.95±5.23	139.55±3.47	172.4	0.001
HR after 4 hours	142.75±6.17	138.5±5.62	139.05±4.62	3.6	0.03
Difference between after 4 hr & before	P=0.3	P=0.400	P=0.103		
RR before nebulization	71.1±8.32	71.25±8.53	65.2±5.12	4.27	0.019
RR after 1/2 hour	69.6±7.93	67.2± 8.97	65.2±4.96	1.74	0.186
RR after 1 hr	69.85±7.88	62.15±9.89	65.6±4.69	4.91	0.011
RR after 4 hours	69.25±7.87	49.5±6.61	66.05±5.13	51.04	0.001
Difference between after 4 hr & before	P=0.47	P=0.001	P=0.323		

HR: Heart rate. RR: Respiratory rate

Table 5. Downes' score (Mean ± SD) before and after nebulization

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	F	P value
Downes' score before nebulization	6.55±0.83	6.35 ±0.93	6.75 ±0.64	1.22	0.302
Downes' score after 1/2 hour	6.35 ±0.88	6.1 ± 0.79	6.55 ± 0.82	1.48	0.237
Downes' score after 1 hr	6.2 ± 0.89	5 ± 0.97	6.3 ±0.73	13.75	0.001
Downes' score after 4 hours	6.18 ±0.69	2.35 ± 1.14	6.35 ±0.67	141.63	0.001
Difference between before 4 hr & after	P=0.13	P=0.0001	P=0.06		

3.6 Duration of Respiratory Support and Duration of Hospital Stay

There was a significant difference ($p < 0.001$) between groups in duration of respiratory

support and duration of hospital stay. Salbutamol group recorded the least duration in both parameters in comparison to the other groups.

Table 6. Duration of respiratory support and duration of hospital stay for the studied groups

Variables	Group I (Epinephrine) n=20	Group II (Salbutamol) n=20	Group III (Saline) n=20	F	P value
Duration of respiratory support (hours)					
Mean ± SD	29.85±6.85	20.15±7.28	50.65±16.18	40.29	0.001
Duration of hospital stay (day)					
Mean ± SD	4.2±0.46	2.8±0.77	4.55±0.83	35.74	0.001

4. DISCUSSION

In an attempt to evaluate the role of inhaled salbutamol versus inhaled epinephrine in the treatment of TTN this study was conducted on 60 neonates (35 males and 25 females) diagnosed clinically and radiologically as TTN.

In this study there was predominance for males than females (58.3%: 41.6%) this was in agreement with [4]; [10] who observed male predominance in TTN. Caesarian section was the mode of delivery of 37 neonates (61.6%) and no recorded neonates had history of PROM (which may need more cases). Eight neonates (0.13%) had history of maternal gestational diabetes while 6 (10%) had history of maternal asthma.

Similarly, [8] found that main risk factors for TTN are cesarean delivery, large birth weight, maternal gestational diabetes, maternal asthma, twin pregnancy, and male gender.

In this study, caesarian section was the mode of delivery of 37 neonates (61.6%) and this is similar to several studies that documented the high incidence of respiratory distress, TTN and NICU admissions in infants born by cesarean delivery before the onset of spontaneous labor [11-17].

Vaginal delivery has two mechanisms by which it decreases the risk of TTN, the first is: mechanical effect as fetal thorax compression during labor leads to the loss of large volumes (25-35%) of liquid from the lung. Although 'vaginal squeeze' during the progression of the chest through the birth canal is thought to be the main physical force, uterine contraction during labor impose fetal postural changes leading to compression of the thorax [18]. The second mechanism is through the release of fetal adrenaline that occurs late in labor which stimulates pulmonary epithelial cells to stop secreting and start absorbing lung fluids. Labor

increases clearance of alveolar fluid even in infants delivered by CS. TTN occurs less frequently in neonates delivered after the onset of labor compared with those delivered before labor [1].

In our study there were 6 asthmatic mothers (10%). Maternal asthma is considered to be an independent factor for TTN. Infants with TTN at birth are at risk of developing asthma or (wheezing) later in life. Genetic predisposition for β -adrenergic hyper responsiveness may cause TTN in newborn period, and asthma/wheezing in older age group. It seems that TTN may be the first sign of asthma [3,19].

The most profound finding in TTN is tachypnea, starting in the first 1 to 2 hours after delivery, and the respiratory rate can reach 60 to 120 breaths/min [6]. Prolonged tachypnea can increase the duration of hospitalization, the use of antibiotics and parental anxiety [20]. [21] determined the respiratory rate over 90 breaths/min at 36th hour after delivery, as a predictive value in terms of prolonged tachypnea.

In our study we observed that the respiratory rate decreased with salbutamol inhalation than control and epinephrine group that was in agreement with [22].

In our study there was transient rise in the heart rate in salbutamol and epinephrine groups. That was in agreement with [10], but was not in agreement with [22], who did not record increase in heart rate.

The duration of respiratory support and hospitalization duration decreased with salbutamol inhalation than control. That was in agreement with [22]. The duration of respiratory support and hospitalization duration decreased with epinephrine inhalation than control. In comparison between salbutamol and epinephrine inhalation, the duration of respiratory support and the duration of hospitalization were less with salbutamol than epinephrine inhalation.

Comparing studied groups after intervention, highly significant lower respiratory rate, Downs' scores, respiratory support and duration of hospital stay was detected in group II (salbutamol group) while no significant difference between groups regarding heart rate after 4 hours from intervention. Similar to our results, [4] found that inhaled salbutamol in infants with TTN, decreases in respiratory rate, and TTN clinical score significantly while non-significant difference regarding heart rate was detected; also they found the improvement in the level of respiratory support was statistically significant with inhaled salbutamol that was in agreement with [22]. On the other hand [10], found no significant difference between inhaled epinephrine and saline inhalation regarding clinical data.

Regarding ABG findings after intervention, PH, PaO₂ and O₂ saturation were significantly higher in group II (inhaled salbutamol), PaCO₂, FiO₂ were significantly lower in group II. No significant difference was detected between groups regarding serum glucose and serum potassium that coincides with [23,24] who said that, serious bronchospasm, arrhythmias, hypokalemia, and hyperglycemia caused by glycogenolysis have been reported rarely. We didn't report any other adverse effects.

Similar to our results [4], found significantly higher PH, PaO₂ and significantly lower PaCO₂, FiO₂ in salbutamol group.

5. CONCLUSIONS

This prospective trial showed that a single dose of inhaled Salbutamol resulted in better outcome in decreasing the respiratory rate, TTN clinical score, lower FiO₂, higher O₂ saturation, decreasing the duration of respiratory support along with the total duration of hospitalization.

Salbutamol inhalation was better than Epinephrine inhalation in decreasing the respiratory rate, TTN clinical score, higher O₂ saturation, and decreasing the duration of respiratory support and the total duration of hospitalization.

6. RECOMMENDATIONS

1. Inhaled salbutamol can be used in treatment of transient tachypnea of newborn to improve respiratory distress and outcome

2. Larger studies are recommended to verify the efficacy of inhaled salbutamol or epinephrine as a therapeutic intervention for this common respiratory condition.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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