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Evaluation of inhaled beta-2 agonist in management of transient tachypnea of the newborn

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Abstract

Background: Transient tachypnea of the newborn (TTN) is a common cause of early neonatal respiratory distress. It is due to delayed clearance of fetal lung fluid.

Aim: To evaluate the effect of inhaled salbutamol, a beta-2 adrenergic agonist (β2AA), in management of TTN and to detect any side effects as a result of using it

Methods: A total of 100 infants with TTN were randomly divided into two groups to receive either inhaled salbutamol (treatment group) or an equal volume of normal saline solution (placebo group) at the time of diagnosis. At enrollment (by the 6th hour), complete blood count, blood glucose, serum potassium (K+), arterial blood gasses, respiratory rate, heart rate, blood oxygen saturation (O_2 Sat), fraction of inspired oxygen (FiO_2), and TTN clinical score were determined for all patients. At 0.5, 1, and 4 h after drug administration, respiratory rate, heart rate, O_2 Sat, FiO_2, and the clinical TTN score were recorded. At 4 h after treatment, arterial blood gasses, serum K+, and blood glucose levels were measured again. The duration of total respiratory support and the duration of hospitalization were recorded as well.

Results: No statistically significant differences existed between both groups in terms of gestational age, birth weight, gender, mode of delivery, Apgar score, or maternal risk factors. The duration of respiratory support and duration of hospitalization were significantly shorter in the treatment (salbutamol) group ($P < 0.0005$, $P < 0.0002$, respectively). In the treatment (salbutamol) group; the respiratory rate, FiO_2 and TTN score were significantly lower after treatment ($P < 0.0001$, $P < 0.0000$, $P < 0.0000$, respectively). Also the PaO_2 significantly increased ($P < 0.0000$) with significant improvement in PH ($P < 0.0001$) and significant reduction in $PaCO_2$ ($P < 0.03$). However, there were no statistically significant differences in heart rates, serum K+, or glucose levels after treatment.

Conclusion: Inhaled salbutamol, a β2AA, was effective in reducing the duration of respiratory support and hospitalization in TTN, with no detected side effects.

Keywords: Newborn, Transient tachypnea, β2-agonist, Salbutamol

Introduction

Transient tachypnea of the newborn (TTN) is the commonest cause of early neonatal respiratory distress. It is due to delayed clearance of the fluid present in the fetal lungs (Hjalmarson 1981; Aslan et al. 2008). At birth, the mature fetal lungs switch from active chloride (fluid) secretion which is important for its growth and development to active sodium (fluid) absorption in response to the rise in circulating fetal catecholamines (Richardson et al. 2005). Catecholamines exert its effect on the beta adrenergic receptors in the alveolar cells resulting in an increase in epithelial Na+-channels (ENaC) and sodium-potassium adenosine triphosphatase (Na+-K+-ATPase) activity (Barker and Oliver 2002). Failure of the switch from fluid secretion to fluid absorption by the fetal lung and an immaturity in the expression of the ENaC may play an important role in the development of TTN (Davies 2004). Stimulation of β-adrenergic receptors by beta-2 adrenergic agonists (β2AA)

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upregulates alveolar epithelial Na+ transport through increasing the activity of ENaC and Na+-K+-ATPase and protein abundance at the plasma membrane (Minakata et al. 1998; Mutlu et al. 2004). Previous studies on animal and human lungs pointed to a potential therapeutic role for β2AA in facilitating resorption of alveolar fluid (Sakuma et al. 1997; Frank et al. 2008). Although a self-limited condition that may resolve within 48–72 h, tachypnea in TTN may be severe and persists, delaying initiation of feeding and increasing the duration of hospitalization (Moresco et al. 2016). The aim of our study was to evaluate the effect of inhaled salbutamol, a β2AA, in management of TTN and to detect any side effects as a result of using it.

Methods

This is a multi-centric study conducted at the neonatal intensive care unit (NICU) of four hospitals (Al-Shorouk, Demashk, Magdy and AL-Safwa) during 2018–2019. A total of 100 infants with TTN were randomly divided into two groups to receive either inhaled salbutamol or an equal volume of normal saline solution placebo at the time of diagnosis. Informed consent was obtained from the parents, and the study protocol was approved by the National Research Centre Ethics Committee. Patients were eligible for enrolment if they were diagnosed with TTN and are < 6 h old. The diagnoses of TTN was according to the criteria of Rawlings and Smith (1984) on the basis of clinical and radiological findings of (1) onset of tachypnea within 6 h after birth; (2) persistence of tachypnea for at least 12 h; (3) chest radiograph indicating at least one of the following: prominent central vascular markings, widened inter-lobar fissure of pleural fluid, symmetrical perihilar congestion, hyperaeration as evidenced by flattening and depression of the diaphragmatic domes or increased anteroposterior diameter, or both; and (4) exclusion of other known respiratory disorders (respiratory distress syndrome, pneumonitis, meconium aspiration syndrome), and non-respiratory disorders (congenital heart diseases, polycythemia, hypoglycemia) likely to cause tachypnea.

At enrollment (by the 6th hour), complete blood count, blood glucose and K+, arterial blood gasses, respiratory rate, heart rate, blood oxygen saturation (O_2 Sat), fraction of inspired oxygen (FiO_2), and TTN clinical score (Table 1) were determined for all patients.

Patients were randomized in a blinded manner to receive one nebulized dose of either 0.9% normal saline solution (group I, placebo), or a solution of salbutamol (group II, treatment) in 0.9% saline solution at a standard dose of 0.15 mg/kg. At 0.5, 1, and 4 h after drug administration, respiratory rate, heart rate, O_2 Sat, FiO_2, and the clinical TTN score were recorded. At 4 h after treatment, arterial blood gasses, serum K+, and blood glucose levels were measured again. The duration of total respiratory support and the duration of hospitalization were recorded as well.

Table 1 Clinical TTN score

Score	0 point	1 point	2 points	3 points
Expiratory grunting	None	Intermittent	Continuous	–
Supraclavicular retraction	None	Mild	Moderate	Severe
Subcostal retraction	None	Mild	Moderate	Severe
Cyanosis	None	At extremities	Central	–
Nasal flaring	None	mild	Moderate	Severe

Statistical analysis

Data analysis was carried out using the standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 17.0 (SPSS Inc., USA). All numeric variables were expressed as mean ± standard deviation (SD). The intergroup comparisons were performed by using an independent-sample *t* test and a one-way analysis of variance and Chi-Square tests for categorical variables. For all tests, a *P* value of less than 0.05 was considered significant.

Results

The study included a total of 100 neonates diagnosed with TTN who were randomly divided into two groups.

Table 2 Demographic data of study groups and maternal risk factors

Variables	Group I (saline)	Group II (salbutamol)	*P* value
Number	46	54	
Sex (M/F)	27/19	32/22	0.995
Gestational age (weeks ± SD)	36.85 ± 1.57	36.73 ± 1.66	0.504
Birth weight (gm ± SD)	2883.15 ± 437.94	2825.87 ± 414.61	0.731
Hemoglobin (g/dl)	15.33 ± 1.49	15.12 ± 1.55	0.481
Weight blood cell count (/mm^3)	16,283 ± 3141	16,591 ± 1884	0.446
Elective cesarean section/NVD	27/19	31/23	0.897
Apgar score (5th min)*	9	9	0.27
Oxygen saturation (%)	88.7 ± 3.98	89.96 ± 3.93	0.15
Duration of respiratory support (h)	61.43 ± 16.81	49.17 ± 15.86	0.0005
Duration of hospitalization (days)	4.76 ± 1.14	3.89 ± 1.08	0.0002
Maternal risk factors			
Maternal age	29.12 ± 4.45	28.53 ± 4.78	0.499
Maternal diabetes	3	5	
PROM	3	2	

*Median. *PROM* premature rupture of membrane

Table 3 Comparison of data before and 4 h after treatment among study groups

Variable	Group I (saline)		*P* value	Group II (salbutamol)		*P* value
	Before	After		Before	After	
Respiratory rate (breath/min)	74.36 ± 8.08	71.47 ± 8.15	0.09	72.11 ± 7.56	62.59 ± 7.43	0.0001
Heart rate (beats/min)	148.32 ± 11.52	146.33 ± 22.28	0.17	144.78 ± 10.34	142.72 ± 10.25	0.13
TTN score*	7 (6–9)	7 (5–9)	0.06	8 (7–10)	3 (3–5)	0.0000
PH	7.28 ± 0.14	7.31 ± 0.09	0.26	7.26 ± 0.13	7.36 ± 0.07	0.0001
FiO_2 (%)*	65(50–75)	60(45–75)	0.06	65(50–80)	30(25–45)	0.0000
PaO_2 (mmHg)	68.04 ± 10.03	71.58 ± 9.98	0.09	67.69 ± 11.19	81.77 ± 10.84	0.0000
$PaCO_2$ (mmHg)	44.21 ± 6.74	46.17 ± 6.42	0.16	45.48 ± 6.53	40.33 ± 6.76	0.03
Serum K (mEq/L)	4.24 ± 0.68	4.37 ± 0.71	0.38	4.36 ± 0.64	4.15 ± 0.61	0.07
Glucose (mg/dl)	79.04 ± 10.17	77.85 ± 9.73	0.29	77.81 ± 10.19	80.26 ± 9.94	0.23

*Median

Group I (placebo; normal saline group) and group II (treatment; salbutamol group) with a mean gestational age (36.85 ± 1.57 SD, 36.73 ± 1.66 SD) and a mean birth weight (2883.15 ± 437.94 SD, 2825.87 ± 414.61 SD) respectively with no statistically significant difference. The demographic characteristics of both groups are shown in Table 2. No statistically significant differences existed between both groups in terms of gender, mode of delivery, Apgar score or maternal risk factors. The duration of respiratory support and duration of hospitalization were significantly shorter in the treatment (salbutamol) group ($P < 0.0005$, $P < 0.0002$, respectively) (Table 2).

Table 3 shows the means for respiratory rates, heart rates, TTN scores, FiO_2, PH, PaO_2, $PaCO_2$, serum K+, and glucose in both groups before and 4 h after treatment. In the placebo (saline) group, there were no statistically significant differences before and after treatment in any of the aforementioned parameters. In the treatment (salbutamol) group; the respiratory rate (Fig. 1), FiO_2 (Fig. 2), and TTN score were significantly lower after treatment ($P < 0.0001$, $P < 0.0000$, $P < 0.0000$, respectively). Also, the PaO_2 significantly increased ($P < 0.0000$) with significant improvement in PH ($P < 0.0001$) and significant reduction in $PaCO_2$ ($P < 0.03$). However, there were no statistically significant differences in heart rates, serum K+, or glucose levels after treatment.

On comparing the two groups together, before treatment, there were no statistically significant differences except for the TTN score which was higher in the salbutamol group ($P < 0.01$). After treatment, the respiratory rates, TTN score, and FiO_2 were significantly lower in the salbutamol group ($P < 0.0000$). Also, there was a statistically significant difference in PH ($P < 0.02$), PaO_2 was significantly higher ($P < 0.0000$), and $PaCO_2$ significantly lower ($P < 0.0004$) in the salbutamol group. No significant differences existed between the two groups after treatment as regards the heart rates, serum K+, or blood glucose (Table 4).

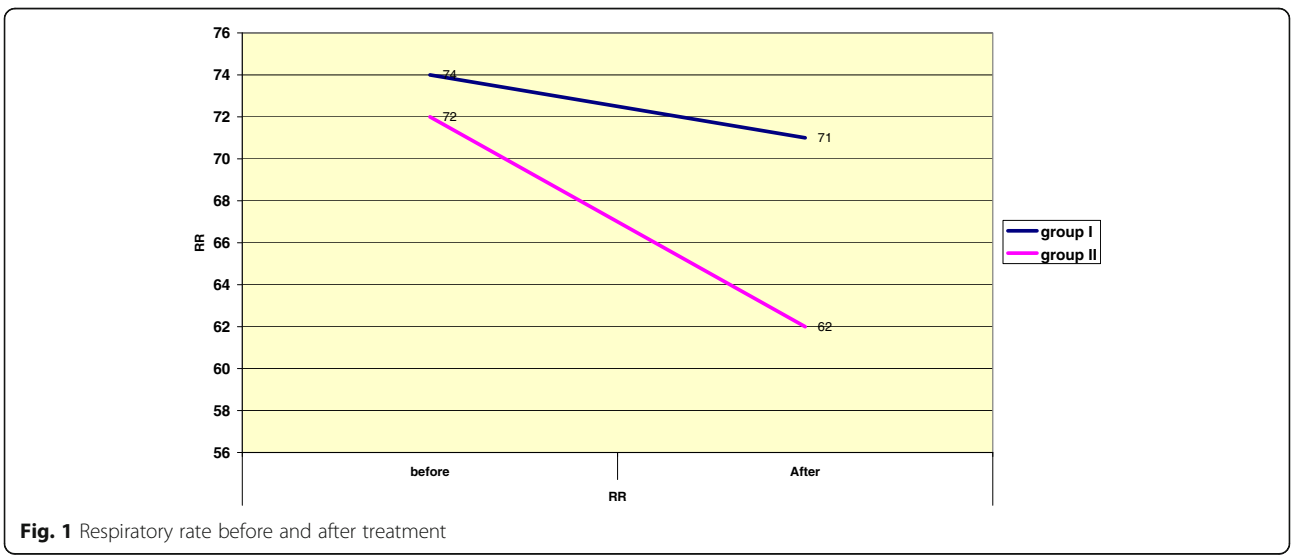

Fig. 1 Respiratory rate before and after treatment

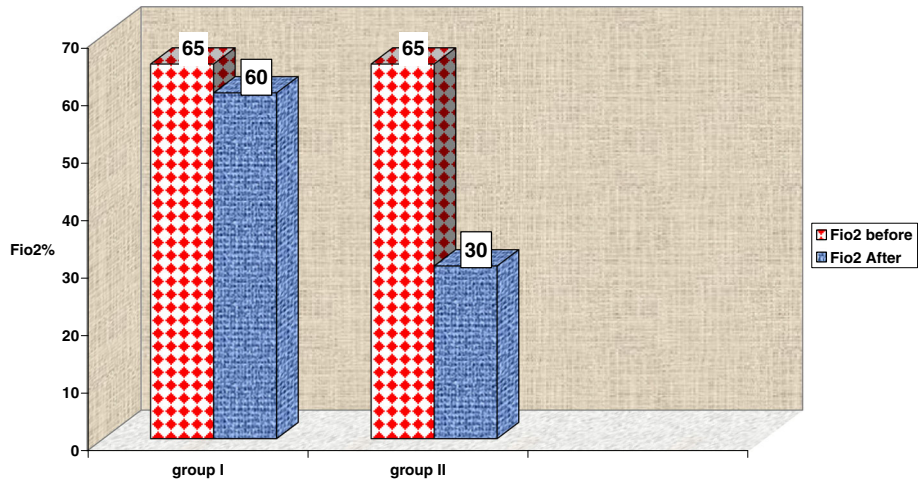

Fig. 2 FiO_2% before and after treatment

Discussion

Although a self-limited condition that presents shortly after birth and usually resolves within 48–72 h, the tachypnea in TTN can be severe and reach 60–120 breath/min (Moresco et al. 2016). Persistent tachypnea can lead to a delay in the start of feeding, increased duration of hospitalization, and unnecessary use of antibiotics (Harding and Hooper 1996). Previously, furosemide, racemic epinephrine, and inhaled β2AAs were studied to detect any potential therapeutic benefits for their use in the management of TTN; furosemide and epinephrine did not show good results, while inhaled β2AAs showed promise in some studies (Moresco et al. 2016; Kao, n.d.; Butchiboyina et al. 2017; Wiswell et al. 1985). The aim of our study was to evaluate the effect of inhaled salbutamol, a β2AA, in management of TTN and to detect any side effects as a result of using it. In this study, the duration of respiratory support and the duration of hospitalization were significantly shorter for those treated with salbutamol than the placebo group. Mohammadzadeh et al. reported a significant shorter duration of respiratory support, hospitalization, and earlier starting of feeding in those treated with salbutamol (Mohammadzadeh et al. 2017). Also, Armangil et al. showed that salbutamol can decrease the duration of hospital stay (Armangil et al. 2011). On the other hand, Kim et al. although reporting a shorter duration of tachypnea and respiratory support, they found no significant reduction in the duration of hospitalization after salbutamol (Kim et al. 2014).

In the present study, the TTN score before treatment was significantly higher and more severe in the treatment (salbutamol) group than the placebo (saline) group, yet it significantly decreased after salbutamol treatment along with a significant reduction in the respiratory rates and FiO_2 in the treatment group. Also, we found a significant rise in PaO_2 with a significant improvement in PH and significant reduction in $PaCO_2$ after salbutamol treatment. This is in consistence with results from other studies (Mohammadzadeh et al. 2017; Armangil et al. 2011) demonstrating that inhaled β2AA was found to improve clinical and laboratory parameters.

Table 4 Comparison between group I and group II before and 4 h after treatment

Variable	Before treatment		*P* value	After treatment		*P* value
	Group I	Group II		Group I	Group II	
Respiratory rate (Breath/min)	74.36 ± 8.08	72.11 ± 7.56	0.15	71.47 ± 8.15	62.59 ± 7.43	0.0000
Heart rate (Beats/min)	148.32 ± 11.52	144.78 ± 10.34	0.06	146.33 ± 22.28	142.72 ± 10.25	0.056
TTN Score*	7 (6–9)	8 (7–10)	0.01	7 (5–9)	3 (3–5)	0.0000
PH	7.28 ± 0.14	7.26 ± 0.13	0.46	7.31 ± 0.09	7.36 ± 0.07	0.02
FiO_2 (%)*	65(50–75)	65(50–80)	0.84	60(45–75)	30(25–45)	0.0000
PaO_2 (mmHg)	68.04 ± 10.03	67.69 ± 11.19	0.66	71.58 ± 9.98	81.77 ± 10.84	0.0000
$PaCO_2$ (mmHg)	44.21 ± 6.74	45.48 ± 6.53	0.19	46.17 ± 6.42	40.33 ± 6.76	0.0004
Serum K (mEq/L)	4.24 ± 0.68	4.36 ± 0.64	0.36	4.37 ± 0.71	4.15 ± 0.61	0.08
Glucose (mg/dl)	79.04 ± 10.17	77.81 ± 10.19	0.31	77.85 ± 9.73	80.26 ± 9.94	0.21

*Median

Similar to other studies (Mohammadzadeh et al. 2017; Armangil et al. 2011), we did not detect any side effects after salbutamol use. No significant differences existed between the two groups after treatment as regards the heart rates, serum K+ or blood glucose.

TTN is common and can sometimes be severe leading to prolonged hospitalization and parent anxiety. The presence of therapeutic options that would decrease the time of hospitalization and save medical resources is important. However, more studies on a larger scale are required before implementing the use of inhaled β2AAs for routine use in TTN.

Conclusion

Inhaled salbutamol, a β2AA, was effective in reducing the duration of respiratory support and hospitalization in TTN, with no detected side effects.

Abbreviations

ENaC: Epithelial Na+-channels; FiO_2: Fraction of inspired oxygen; K+: Potassium; Na+: Sodium; Na+-K+-ATPase: Sodium-potassium adenosine triphosphatase; NICU: Neonatal intensive care unit; O_2 Sat: Blood oxygen saturation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; TTN: Transient tachypnea of the newborn; β2AA: Beta-2 adrenergic agonist

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Authors' contributions

AT contributed to the idea (concept) of the study, study design, interpretation of data, and writing the manuscript and is the corresponding author. MA contributed to the collection of cases, and revised and approved the manuscript. TF contributed to the collection of cases, analysis of data, and revised and approved the manuscript. MS contributed to the collection of cases. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Informed consent was obtained from the parents, and the study protocol was approved by the National Research Centre Ethics Committee.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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