

THE ROLE OF INHALED B2-ADRENERGIC AGONISTS IN TREATMENT OF TRANSIENT TACHYPNEA OF THE NEWBORN

By

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ABSTRACT

Background: *Transient tachypnea of the newborn (TTN) is a common cause of respiratory distress in the neonatal period. There are few data regarding the pharmacotherapy for the management of TTN. Previous studies documented the therapeutic role for the beta2 agonists in TTN by accelerating the clearance of excessive fluid from the alveolar space. The aim of present study was to assess the effect of salbutamol on major clinical course including duration of oxygen therapy and improvement of respiratory symptoms.*

Objectives: *to evaluate the efficacy of inhaled salbutamol, a beta-2 adrenergic agonist, for the treatment of transient tachypnea of the newborn and to determine whether inhaled salbutamol is safe in newborn infants born between 36th and 39th weeks.*

Methods: *It is randomized controlled clinical trial, on 100 neonates who was admitted immediately or shortly after birth due to persistence of tachypnea to neonatal intensive care unit (NICU) of Al Hussein and Bab al sharia university hospitals. (50 on salbutamol therapy(group A), 50 As control (group B) with RD born between 36th and 39th weeks of gestational age infants will be randomized in a blinded manner to receive one nebulized dose of salbutamol 0.15 mg/kg in 0.9% saline solution in addition to oxygen and IV fluids (group A) or received only oxygen and IV fluids (group B) .The response to inhaled salbutamol will be evaluated by determining respiratory rate, heart rate, clinical score of transient tachypnea of the newborn, level of respiratory support, before and at 30 minutes and 1 and 4 hours after drugs therapy.*

Results: *There is significant decrease in respiratory rate and TTN score in (group A) 4 hours after nebulized salbutamol.*

Conclusion: *Inhaled salbutamol treatment was effective in TTN without adverse events.*

Key words: *Transient Tachypnea of the Newborn, Oxygen Therapy, Salbutamol Inhalation.*

INTRODUCTION

Transient tachypnea of the newborn (TTN) or wet lung is a common physiologic lung disorder characterized by pulmonary oedema secondary to clearance delay of fetal alveolar fluid immediately after birth. TTN is a common cause of dyspnoea in the newborn. The incidence rates of TTN are 4.0% to 5.7% among term infants and 10.0% in premature infants (**Liu et al., 2014**).

The risk factors associated with TTN includes; prematurity, male sex, large birth weight, Meconium-stained amniotic fluid, caesarean section delivery (esp. elective caesarean), gestational diabetes, maternal chorioamnionitis and maternal asthma (**Hansen et al., 2008**).

TTN is a benign, self-limited clinical condition in most patients but rarely could result in severe complications such as severe hypoxia and death which is called "malignant TTN". For the management of TTN, it requires cardiorespiratory monitoring; supportive care in the neonatal intensive care unit (NICU) includes: maintaining a neutral thermal environment and providing nutrition, preclude oral feeding, low-percentage

supplemental oxygen. Beginning the prophylactic antibiotics coverage is also suggested in literature until blood cultures are reported negative (**Weintraub et al., 2013**).

There are few data regarding pharmacotherapy for the management of TTN. Previous studies suggested inhaled epinephrine, oral or intravenous and inhaled furosemide, beta2 agonist inhalation and fluid restriction but the most appropriate treatment approach is still matter of controversy (**Kassab et al., 2013**).

Randomized controlled trials are needed to confirm the feasibility and safety of the most proper approaches in this field. We aimed to conduct a randomized clinical trial of the efficacy of inhaled salbutamol for the treatment of TTN. Our primary objective was to assess the effect of salbutamol on major clinical course including duration of oxygen therapy and improvement of respiratory symptoms. Additional analysis focused on the time of initiation of first enteral feeding and duration of hospitalization.

PATIENT AND METHODS

This study included one hundred (100) neonates between

36th -39th week's gestation who were admitted immediately or shortly after birth due to persistence of tachypnea to neonatal intensive care unit (NICU) of Al Hussein and Bab Al Sharia university hospitals.

Neonates were randomized into the study by a random number table sequence (i.e. patients 1, 3, 5.etc to nebulized salbutamol group (A) and alternatively patients 2, 4, 6.etc to only oxygen and IV fluids group). The allocations were contained in opaque sequentially numbered sealed envelopes.

They randomly divided into two groups:

1. Group A: Fifty neonates received once nebulized salbutamol (0.15 mg/kg over 20 minutes) in addition to oxygen and intravenous fluids (IV fluids) as 10% dextrose in water at 60 to 80 mL/kg per day.

2. Group B: A control group of fifty neonates received only oxygen and IV fluids at 60 to 80 mL/kg per day.

Inclusion criteria:

1. The G.A between 36th - 39th weeks.
2. Delivered by caesarean section or vaginal delivery.

TTN was diagnosed by:

1. Clinical:

Onset of tachypnea (respiratory rate exceeding 60 breaths/min, retraction, nasal flaring or grunting) within 6 hours after birth.

Persistence of tachypnea for at least 12 hours.

2. Radiological:

Radiological signs of at least one of the following in the chest x-ray:

- Prominent central vascular markings.
- Widened interlobar fissures of pleural fluid.
- Symmetrical perihilar congestion.
- Hyperaeration as evidenced by flattening and depression of the diaphragmatic domes or increased antero posterior diameter or both.

Exclusion criteria:

Any newborn with one of the following:

1. Respiratory distress syndrome (reticulogranular patterns on the chest radiograph and in need for surfactant therapy).
2. Sepsis and pneumonia (perinatal risk factors, WBC < 5,000/mm³, immature-to-total neutrophil (I: T) ratio > 0.25, positive C-reactive protein, and

focal infiltration on chest radiography).

3. Meconium aspiration syndrome (meconium staining of the skin and abnormal chest radiography findings as irregular pattern of increased density throughout the lung).
4. Apparent Congenital cardiac diseases as Persistent pulmonary hypertension of the newborn (the level of pre ductal oxygen saturation is $> 5\%$ above post ductal oxygen saturation).
5. Perinatal asphyxia (low APGAR at 5 minutes and evidence of acute hypoxic compromise with acidemia) (Adriani et al., 2006).
6. Congenital malformations (e.g Diaphragmatic hernia).
7. Non respiratory disorders (hypocalcaemia, persistent hypoglycaemia, polycythaemia, metabolic acidosis etc.).

All the neonates included in the study were subjected to the following:

I. Full history taking:

With special emphasis on:

1. Perinatal history: Maternal medical disorders during pregnancy especially preeclampsia, diabetes mellitus, Antenatal corticosteroids, Gestational age.
2. Natal history: Mode of delivery, perinatal asphyxia, Meconium aspiration.
3. Postnatal history: Birth weight, Resuscitation data and delivery room interventions, Apgar score at 1 and 5 minutes resuscitation.

II .Clinical examination:

- Estimation of gestational age using modified Ballard score (Meherban et al., 2015).
- Estimation of birth weight, length and head circumference at birth and plotted on growth charts (WHO et al., 2006).
- Vital Signs: heart rate, respiratory rate and core temperature.
- Pre ductal and post ductal oxygen saturation.
- TTN clinical 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

(Armangil et al., 2011)

Interpretation:

- 0 - 5 mild TTN.
- 5 - 10 moderate TTN.
- 10 - 15 severe TTN.

- Chest examination.
- Cardiac examination.
- Abdominal examination.
- Neurological examination.
- O2 saturation by pulse Oximetry on admission.

III .Investigations:

A.Laboratory:

- Arterial blood gases.
- Complete blood count.
- C–Reactive protein (CRP).

- Serum potassium (K) and sodium (Na).
- Serial random blood sugar measurements.

B. Radiological:

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

IV. Intervention:

To all the studied newborns:

- Empiric use of antibiotics.
- The intravenous fluids were given as 60-80 ml/kg/d for the first postnatal day.

Inhaled salbutamol was administered once to fifty patients (group A).

The standard dose of salbutamol was 0.15 mg/kg/dose. Given with nebulizer with continuous flow of oxygen at 5 to 6 L/min. One dose was administered over the course of 20 minutes.

Treatment was stopped if any patient develops tachycardia or an arrhythmia.

- The response to salbutamol therapy was evaluated:

at 30 minutes, 1 and 4 hours by:

- Determining respiratory rate.
- Clinical score of transient tachypnea of the newborn.
- Level of respiratory support.
- Oxygen saturation by pulse oximeter.
- Four hours after salbutamol nebulization, the following was evaluated for both groups
 - Arterial blood gases (pH, PaCO₂, PaO₂, and SO₂).
 - Serum K⁺
 - Blood Glucose level

- The Duration of total respiratory support:

Was calculated in hours as a total oxygen support via the incubator, nasal cannula, oxygen head box or nasal continuous positive airway pressure.

Ethical consideration:

- Written Parent consent for the study was obtained before the study.
- Approval of the local ethical committee in the pediatrics department, college and university were obtained before the study.
- The author's declared no potential conflict of interest with respect to the research & publication of this article.
- All the data of the patient & results of the study are confidential & the patient has the right to keep it.
- The authors received no financial support for the research & publications of the article.

RESULTS

Table (1): Comparison of Demographic Data between the study Groups

	group A(salbutamol) (N:50)	group B(control) (N:50)	P value
	Mean(±SD)	Mean(±SD)	
Gestational Age	37.76(±0.93)	37.8(±0.65)	0.86
Birth Weight (gms)	3094.4(±193.28)	3019.4(±210.51)	0.196
Skull Circumference (cms)	33.9(±0.43)	33.76(±0.5)	0.297
Length (cms)	48.14(±0.84)	48.06(±1.01)	0.762

There was no significant difference regarding demographic characters between both groups.

Table (2): Comparison of Clinical Data between the study Groups before Supportive Treatment

	Group A(salbutamol) (N:50)	group B (control) (N:50)	P value
	Mean(±SD)	Mean(±SD)	
Oxygen Saturation at Birth	92.2(±2.1)	91(±2.12)	0.053
Respiratory Rate / M	75.12(±4.84)	74.68(±6.47)	0.787
Heart Rate/M	144.08(±7.46)	142.24(±9.6)	0.453
Rectal Temperature(C)	36.92(±0.18)	36.84(±0.33)	0.291
TTN Clinical Score	9.12(±0.93)	7.92(±0.95)	< 0.001
Capillary Refill Time in (Seconds)	2(±0)	2(±0)	---
Pre ductal O2 Sat	91.8(±1.87)	91(±2.04)	0.274
Post ductal O2 Sat	91.37(±1.78)	90.54(±2.3)	0.279

There is significant difference in TTN score between groups before initiation of study. Accidentally, salbutamol group

cases were worse more than control group cases in TTN score before initiation of study in spite of randomization.

Table (3): Comparison of Blood gases, serum K and blood glucose Data between the study Groups on Admission

	group A(salbutamol)	group B (control)	P value
	Mean(\pmSD)	Mean(\pmSD)	
PH	7.31(\pm 0.08)	7.34(\pm 0.05)	0.122
PaCo2	43.2(\pm 9.91)	36.84(\pm 8.78)	0.09
PaO2	79.24(\pm 43.39)	103.72(\pm 54.15)	0.084
HCO3	17.34(\pm 1.28)	18.95(\pm 2.67)	0.08
BE	8.3(\pm 1.43)	7.04(\pm 2.55)	0.055
SO2	74.8(\pm 20.01)	76.08(\pm 20.31)	0.823
K	4.59(\pm 0.4)	4.29(\pm 0.63)	0.059
Blood glucose	95.32(\pm 14.79)	96.71(\pm 16.91)	0.761

No significant difference between both groups regarding blood gases, serum K and blood glucose data on Admission.

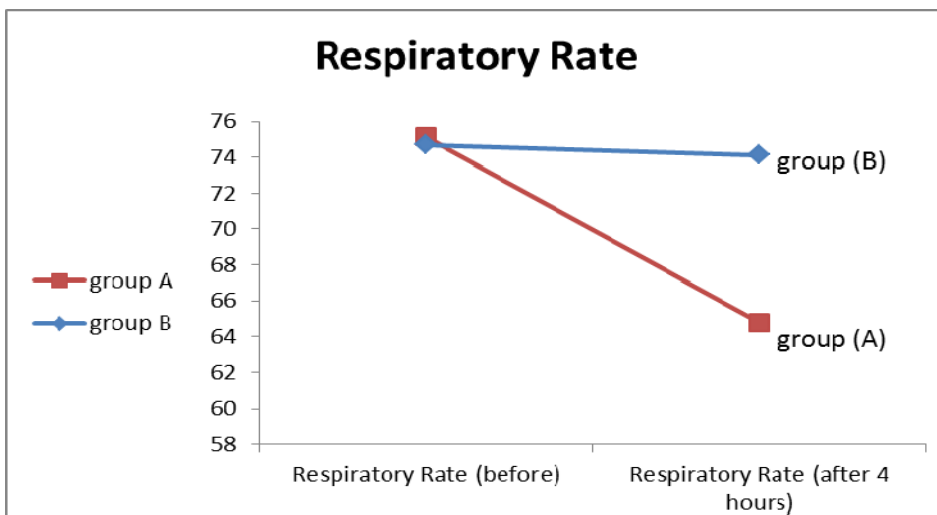
Table (4): Comparison of Clinical and Laboratory Data between the study Groups 4 hours After Management

	group A (salbutamol) N:50	group B (control) N:50	P value
	Mean (±SD)	Mean (±SD)	
Respiratory Rate / M	64.80 (±4.14)	74.12 (±5.85)	< 0.001
Heart Rate / M	140.61 (±8.25)	141.24(±7.6)	0.353
Oxygen Saturation%	98.68 (±0.63)	98.44 (±0.92)	0.285
TTN Clinical Score	5.08 (±1.58)	7.32 (±0.85)	< 0.001
ABG:			
PH	7.40 (±0.05)	7.36 (±0.04)	0.073
PaCo2 (mmHg)	36.52 (±6.42)	34.32 (±7.14)	0.255
PaO2 (mmHg)	90.36 (±44.9)	105.72 (±54.9)	0.285
Serum K(Mel/L)	4.73 (±0.34)	4.72 (±0.53)	0.954
Blood glucose(mg/dl)	110.04 (±10.43)	112.00 (±19.72)	0.733

Four hours after management there was significant decrease (P < 0.001) in respiratory rate which is 64.80 (± 4.14) in salbutamol group versus 74.12 (±5.85) in control group ,Also

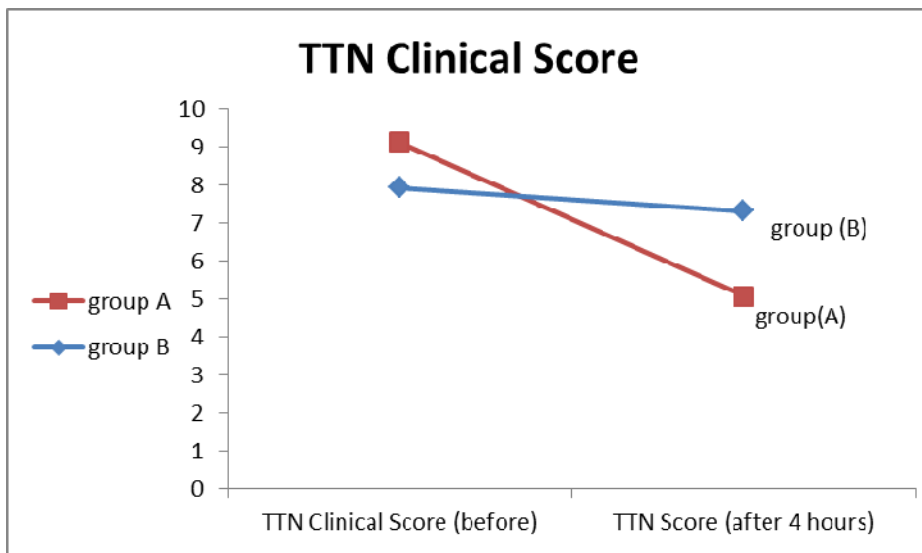
there was significant decrease (P < 0.001) in TTN score which is 5.08±1.58 in salbutamol group versus 7.32±0.85 in control group 4 hours after enrollment in study.

Figure (1): Comparison between the study Groups in Respiratory Rate Before and 4 hours After Management



This figure show improvement in Respiratory rate in group (A) after management but no improvement in group (B).

Figure (2): Comparison between Groups in TTN Score Before and 4 hours After Management



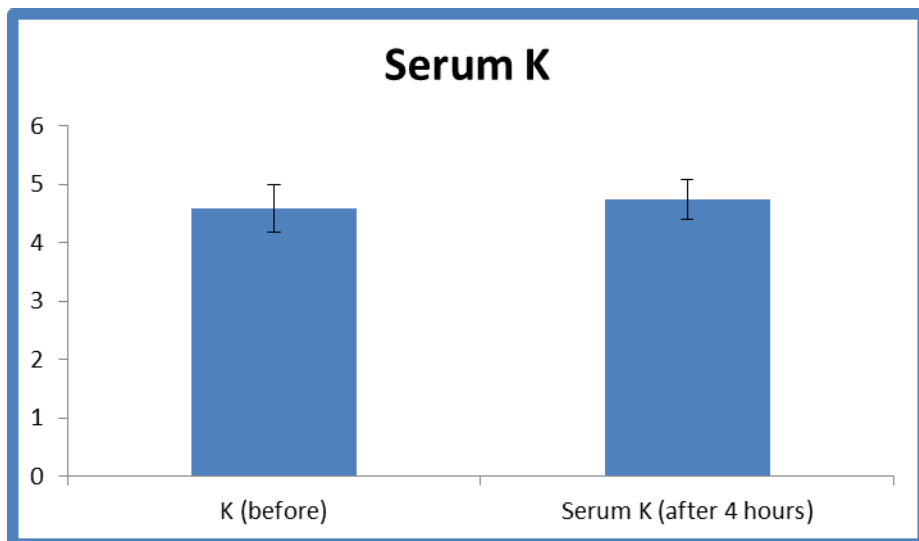
This figure show improvement in TTN Score in group (A) after management but no improvement in group (B).

Table (5): Comparison of Supportive Management Duration since Admission till Discharge between the study groups

	group A(salbutamol)		group B (control)		P value
	Number	Mean (\pm SD)	Number	Mean (\pm SD)	
Total Duration on oxygen (hours)	50	61.12(\pm 19.31)	50	78.24(\pm 21.9)	0.005
Duration on NCPAP (hours)	32	22.24(\pm 13.09)	25	35.76(\pm 18.3)	0.004
Duration on nasal cannula (hours)	10	14.72(\pm 11.53)	20	18.08(\pm 12.1)	0.32
Duration on Head Box (hours)	8	10.88(\pm 4.76)	5	11.44(\pm 3.24)	0.629
Duration on Incubator Oxygen (hours)		13.28(\pm 7.46)		12.96(\pm 7.68)	0.882
Duration of Hospitalization (days)		3.32(\pm 0.91)		4.68(\pm 1.16)	< 0.001
Time before initiating enteral feeding (hours)		30.16(\pm 11.73)		40.56 (\pm 13.1)	0.005

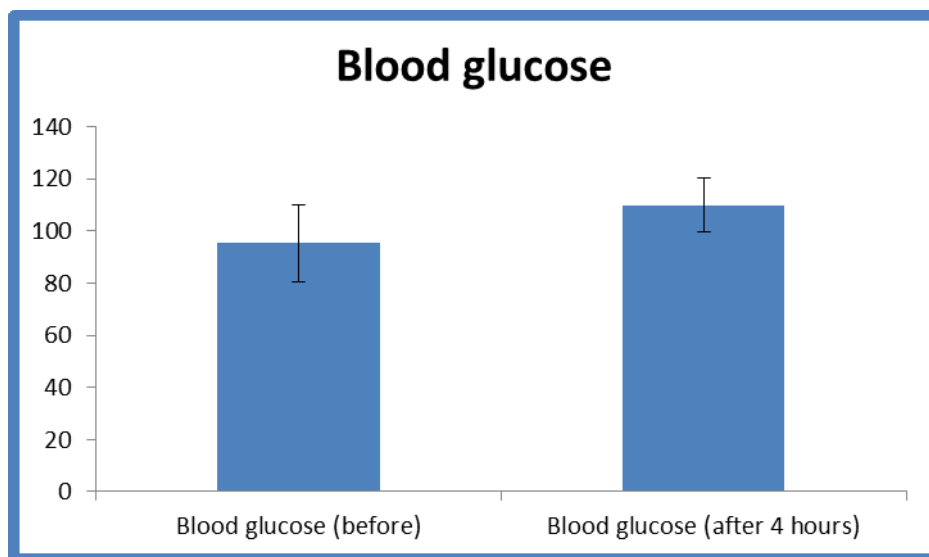
There is significant decrease in total duration of oxygen therapy, hospitalization and time before initiating enteral feeding in hours in group (A).

Figure (3): Serum K Level Before and After Nebulized Salbutamol



No significant difference regarding K level before and after Salbutamol.

Figure (4): Random Blood Sugar Level Before and After Nebulized Salbutamol



No significant difference regarding Random Blood Sugar level before and after nebulized Salbutamol.

DISCUSSION

The alveolar epithelium in the fetal lung secretes chloride into the alveolus. Chloride enters the lung epithelial cell across the basolateral membrane via a Na⁺/K⁺/2 Cl⁻ co-transporter. The chloride ions are secreted into the alveolus by various chloride channels. The potassium ion extrudes through basolateral potassium channels. Sodium follows chloride through paracellular pathways, with water flowing between or through cells via aquaporins, thus helping to maintain adequate lung fluid (Guglani et al., 2008).

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 sodium-potassium adenosine triphosphatase (Na⁺-K⁺-ATPase) activity (Barker and Olver, 2002).

The inability of the fetal lung to switch from fluid secretion to fluid absorption and the immaturity in the expression of the ENaC may play an important role in the development of TTN (Davies, 2004).

In our study regarding manifestation of respiratory distress there was statistically

significant decrease in Respiratory rate in salbutamol group while there was no significant decrease in respiratory rate in control group.

In Agree with our study .A study done by (Monzoy-Ventre 2015) reported clinical improvement and reduction in respiratory rate following salbutamol administration.

Regarding TTN clinical score There was also decrease in TTN clinical score from 9.12±0.93 to 5.08±1.58 in salbutamol group versus no significant decrease (P=0.102) in TTN clinical score from 7.92±0.95 to 7.32±0.85 in control group.

In agree with our study Turkish study reported significant decrease (P < 0.001) in TTN clinical score before (median=8) and 4 hours after nebulized salbutamol (median=2.5) in salbutamol group (Armangil 2011).

Regarding blood gases findings in the current study, there was significant improvment regarding pH and PaO₂ before and 4 hours after nebulized salbutamol with P value=0.051 and P=0.053 respectively.

In agree with our study, (Armangil 2011) found that the mean pH, PaO₂ values were better in the salbutamol group when

compared with the control group ($P < 0.05$) after management.

Regarding duration of respiratory support and the total duration of hospitalization. Comparing two groups after respiratory support in our study, the total duration of oxygen treatment in hours and the total duration of hospitalization in days were significantly shorter in salbutamol group (61.12 ± 19.31 hours) and (3.32 ± 0.91 days) than in control group (78.24 ± 21.9 hours) and (4.68 ± 1.16 days) with $P = 0.005$ and $P < 0.001$ respectively. The time before initiating enteral feeding in hours was significantly shorter in salbutamol group (30.16 ± 11.73 hours) than in control group (40.56 ± 13.1 hours) with $P = 0.005$.

Unlike our study, Armangil 2011 found no significant difference in total duration of respiratory support in hours between salbutamol group (median=30) and control group (median=48) with $P = 0.112$. But, the total duration of hospitalization in days was significantly shorter in salbutamol group (median=4) than in control group (median=6) with $P = 0.002$.

In Agreement with our study, Korean study done by Kim 2014 reported that the duration of

supplemental oxygen therapy and the duration of empiric antibiotic treatment were significantly shorter in the salbutamol treated group with P value < 0.01 and 0.04 respectively. The duration of tachypnea was shorter in patients receiving inhalational salbutamol therapy, although this difference was not statistically significant $P = 0.37$.

Unlike our study, the Korean study found that the duration of tachypnea was shorter in patients receiving salbutamol inhalation therapy, although this difference was not statistically significant $P = 0.37$. Also, they found no significant difference in total duration of hospitalization in days between salbutamol group (8.5 ± 3.9) and control group (8.8 ± 3.2) with $P = 0.58$.

As regards safety of salbutamol, the current study showed notable increasing in heart rate 30 minutes after nebulized salbutamol. However, there was no significant difference regarding heart rate before (144.08 ± 7.46 bpm) and 4 hours after nebulized salbutamol (140.61 ± 8.25 bpm) with $P = 0.062$ in salbutamol group.

As salbutamol can cause hypokalaemia, serum potassium level was followed before and after therapy. Also random blood

sugar was followed for exclusion of hypoglycaemia as a cause of respiratory distress.

We didn't find significant difference regarding serum potassium level before (4.59 ± 0.4) and 4 hours after nebulized salbutamol (4.7 ± 0.3) with $P=0.112$. There was an increase in blood glucose in salbutamol group from (95.32 ± 14.79 mg/dl) to (110.04 ± 10.43 mg/dl) 4 hours after nebulized salbutamol with no statistical significance ($P = 0.083$). This increase of blood glucose level after nebulized β_2 -agonists can be explained by hepatic glycogenolysis and gluconeogenesis which are stimulated by β_2 -agonists which also increase muscle glycogenolysis and produce lactate (Stratakos et al., 2002).

In agree with our study, Armangil 2011, Kim 2014 and Monzoy-Ventre 2015 reported no adverse effects in salbutamol groups.

Unlike our study, Armangil 2011 found no significant difference detected between 2 groups regarding serum blood glucose before and 4h after inhaled therapy.

CONCLUSION

Our randomized-controlled trial indicated that inhaled

salbutamol could result in shorter duration of respiratory support and hospitalization and earlier initiation of enteral feeding in TTN patients with moderate to severe respiratory symptoms without exposing to any adverse effects during follow up.

RECOMMENDATIONS

1. Salbutamol nebulization can be attempted alone to decrease the duration of hospital stay and the severity of TTN, to improve neonatal outcome.
2. Further large scale studies are necessary to confirm the safety of inhaled salbutamol in this common respiratory condition.
3. Further studies are necessary to show the efficacy of early use of inhaled salbutamol shortly after birth in prevention of admission to NICU due to TTN.
4. Respiratory morbidity is more common in infants delivered by elective caesarean section compared to intended vaginal delivery even in term infants .Therefore, delaying elective cesarean section until 39 weeks or later is recommended (Signore and Klebanoff, 2008).

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دور استنشاق منبهات بيتا الثنائيه في علاج التسارع التنفسي العابر لدي حديثي الولادة

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تعتبر مضاعفات الجهاز التنفسي للأطفال حديثي الولادة مكتملي النمو شائعة والسبب الاكثر شيوعا لصعوبه التنفس لحديثي الولاده هو سرعة التنفس المؤقتة لدي حديثي الولاده حيث تتراوح نسبة حدوثه من نصف بالمئه الي ٢,٨٪ من جميع المواليد الجدد. يعد سرعة التنفس المؤقتة لدي حديثي الولاده مرض حميد وغالبا ما يحدث شفاء عند عمر من يومين الي خمسه أيام. في الحالات الشديده من سرعة التنفس المؤقتة لدي حديثي الولاده قد تحدث مضاعفات مثل إسترواح الصدر، وقد يؤدي الي الوفاة. ويعتقد ان سرعة التنفس المؤقتة لدي حديثي الولاده قد ينتج من تأخر امتصاص السوائل من الرئتين وهو ما يمثل مشكله تشخيصية وعلاجه في وحده العناية المركزه لدي حديثي الولاده.

الهدف من الرسالة:

الهدف من هذه الدراره هو تقييم فعاليه وسلامة استنشاق السالبيوتامول احد منبهات بيتا الثنائيه الأدريناليه في علاج سرعة التنفس المؤقتة لدي حديثي الولاده وما اذا كان امنا في الاطفال حديثي الولاده.

المرضي وطرق البحث:

اشتملت الدراره علي ١٠٠ من حديثي الولاده الذين يعانون من سرعة التنفس المؤقتة وتم حجزهم بوحدة العناية المركزه لحديثي الولاده بمستشفى قد تم تشخيصهم علي اساس اكلينيكي وعمل الأشعة السينيه.

معايير الاستبعاد:

- متلازمه ضيق النفس.
- الاتهاب الرئوي وتعفن الدم.

- العيوب الخلقية للقلب.
- إختناق الولادة.
- العيوب الخلقية.
- الأمراض الغير تنفسية مثل نقص الكالسيوم والسكر بالدم وكثرة كرات الدم الحمراء.

وقد خضع جميع المرضى في هذه الدراسة الي:

اخذ التاريخ الكامل حول: عمر الحمل , مضاعفات أثناء الولادة وبعد الولادة, التاريخ الطبي والتوليد , طريقة الولادة.

الفحوصات:

صورة دم كاملة, بروتين سي التفاعلي ومعياره, تحليل نسبة الغازات بالدم من الشعيرات الدموية.

وقد تم اعطاء ساليوتامول عن طريق الاستنشاق بالاضافة الى المحاليل الوريدية والدعم التنفسي الي المجموعه أ وعددها ٥٠ من الاطفال حديثي الولادة بينما تم اعطاء المحاليل الوريدية والدعم التنفسي فقط الي المجموعه ب و عددها ٥٠ من الاطفال حديثي الولادة في الفتره بين ٣٦ و ٣٩ اسبوعا من الحمل والذين يعانون من سرعة التنفس المؤقتة لدي حديثي الولادة وتم تقييم الاستجابة لعلاج الساليوتامول عن طريق حساب كل من معدل النفس والنماتج الاكلينيكي الخاص بالإسراع التنفسي العابر لدي حديثي الولادة.تم تسجيل مستوي دعم التنفس والاكسجين الجزئي أثناء الشهيق وذلك بعد نصف ساعه وساعه كامله واربع ساعات .وقد تم تسجيل مدة الدعم الكلي للتنفس ومستوي دعم التنفس بالنسبة لمدته الوجود بالعنايه المركزه لحديثي الولادة.

بعد مقارنه مجموعه الدراسة بعد التدخل تم الكشف عن تحسن ذو دلالة احصائية في المجموعه المستخدمة للدواء وذلك في العد التنفسي وفترة الاقامة بالمستشفى والاحتياج للدعم بالاكسجين في حين لا يوجد فرق كبير بين الجماعات بشأن معدل ضربات القلب او نسبة البوتاسيوم بعد ٤ ساعات من التدخل.