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Effects of Inhaled Salbutamol on Transient Tachypnea of the Newborn: A Clinical Trial

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Background: One of the most common causes of respiratory distress in newborns is transient tachypnea of the newborn (TTN). Salbutamol is often suggested to increase the rate of pulmonary fluid absorption in newborns with TTN. This study hence aimed to evaluate the efficacy of inhaled salbutamol in TTN management.

Methods: This double-blind clinical trial was conducted on 52 newborns admitted to the NICU of Fatemieh Hospital of Hamadan, Iran. The newborns were randomly assigned to two groups of equal members: one group received 2 ml of nebulized sodium chloride (control group) and the other group was treated with 0.1 mg/kg of salbutamol (treatment group). The clinical outcomes were then compared before and 0.5, 1, and 4 hours after the intervention. The data were recorded in a checklist and then were statistically analyzed in SPSS-16: the significant level was decided to be $P<0.05$.

Results: The comparison of TTN scores revealed a significant difference between the two groups one hour ($P=0.005$) and four hours ($P<0.005$) after the intervention. Moreover, the mean fraction of inspired oxygen one hour after the intervention was 53.3±6.6 in the treatment group and 57.7±7.5 in the control group ($P=0.022$). The mean duration of respiratory support in the treatment and control groups was 2.4±2.7 and 3.1±0.8 days, respectively ($P=0.002$). The findings suggested no statistically significant difference between the two groups regarding the adverse effects, length of stay (LOS), duration of antibiotics intake, oral feeding resumption time, and maximum oral feeding time ($P>0.05$).

Conclusion: The study results indicated that inhaled Salbutamol significantly decreased the TTN clinical score, oxygen demands, and duration of respiratory support, whereas there was no significant difference between the groups in terms of LOS.

Keywords: Newborns; Respiratory distress; Salbutamol; Transient tachypnea

Introduction

TTN is one of the most common respiratory problems caused by inadequate or delayed clearance of fetal pulmonary fluid.[1] It is characterized by a respiratory rate greater than 60 breaths per minute (BPM) and respiratory distresses manifested by grunting, flaring, and retractions.[2] This problem necessitates the admission of newborns to the neonatal intensive

care unit (NICU), the administration of antibiotics, mechanical ventilation, mother-child separation, and breastfeeding difficulties.[3]

The incidence of TTN ranges between 0.5% and 2.8% in all deliveries.[4] Male gender, macrosomia, gestational diabetes, gestational asthma, preterm birth, perinatal asphyxia, and cesarean sections are the main risk factors for TTN.[5] Previous studies have reported that the risk of TTN in preterm newborns was higher than in term ones. This was especially more common in newborns delivered through cesarean sections.[6] In general, newborns with TTN need to be admitted to NICUs.[7] A chest X-ray technique can be used to diagnose TTN. This method demonstrates an increase in diffuse parenchymal infiltrates caused by fluid in the interstitium, interlobar fissures, and, occasionally, pleural effusions.[8] The most common methods for diagnosing and monitoring TTN are chest radiography, laboratory tests, and close cardiorespiratory monitoring.[9]

TTN clinical features manifest shortly after birth or a few hours later. This situation arises because of the newborn's inability to absorb pulmonary fluid and immaturity in the expression of the epithelial Na^+ channels (ENaC). The fetal catecholamines activated through β-adrenergic receptors, active sodium (Na^+) absorption via enhanced ENaC, and sodium-potassium adenosine triphosphatase activity all influence pulmonary fluid release. By increasing the activity of ENaC and Na^+/K^+-ATPase, beta-2 adrenergic agonists (2AA) can stimulate the β-adrenergic receptors (2AR) for the regulation of active Na^+ transport required to remove excess fluid from alveolar airspace.[10] It is noteworthy that β2AA plays a vital role in increasing the resolution of alveolar pulmonary edema. As a β2AA, inhaled salbutamol is recommended to be used to increase the rate of fetal pulmonary fluid absorption in newborns with TTN. This study hence aims to evaluate the efficacy of inhaled salbutamol in TTN management and to investigate whether inhaled salbutamol is a safe medicine for newborns with TTN.

Methods

A double-blind clinical trial was conducted on 52 newborns admitted to the NICU of Fatemieh Hospital of Hamadan, Iran.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the gestational age between 34 and 37 weeks, (2) tachypnea with above 60 BPM during the first six hours of life, continuing for 12 hours, and (3) diagnosis of TTN based on Chest X-ray findings, including at least one of the following signs: lung hyperinflation, prominent vascular/perihilar marking, fluid-filled interlobar fissure, fluffy bilateral infiltration, and pulmonary edema.

The exclusion criteria were also as follows: (1) respiratory distress syndrome (RDS) (reticulogranular patterns or white lung on chest x-ray or surfactant use), (2) meconium aspiration syndrome (history of meconium disposal or patchy infiltration on chest x-ray), (3) sepsis (prenatal infection risk factors, 5000 < WBC > 15000/mm3, positive C-reactive protein, positive blood culture, and focal infiltration on chest x-ray), (4) congenital heart defects (based on echocardiography), (5) non-respiratory causes of tachypnea (i.e., hypocalcemia, persistent hypoglycemia, and polycythemia), (6) the history of maternal substance abuse, and (7) death during the study.

Study design

Assuming the size effect of 0.80 for LOS in NICU, an alpha error of 0.05, and a test power of 80%, the sample size was determined to be 26 in each group. The required data, including CXR, echocardiography, serum biochemistry (i.e., glucose and calcium), and hemoglobin (Hb) level, were collected from all participants. The purposive sampling method was used to select the participants. The randomization process was carried out using the permuted block randomization method. The block size and allocation ratio for this purpose were 5 and 1:1, respectively. Before assigning the participants to two groups, the random allocation sequence was concealed in sealed opaque envelopes. The evaluator was blinded to the evaluation processes in this study, and the newborns were randomly divided into two groups. It was accomplished through the use of the block randomization method and hiding random allocation. It is worth noting that the specialists in this study were not aware of the medications (sodium chloride alone or a combination of sodium chloride and salbutamol).

The data were collected using the special demographics and clinical information forms and recorded in a researcher-made checklist. A total of 60 newborns with TTN entered the study, but eight newborns (four from the control group and four from the treatment group) were excluded from the study during the intervention for several reasons, including cardiovascular diseases, sepsis, and RSD. It is noteworthy that no cases were excluded due to tachycardia or death. Finally, a total of 52 newborns (n=26 in each group) continued the study to the end (Diagram 1). Based on Rawlings and Smith's criteria, tachypnea was identified as the principal manifestation of TTN.[2]

Furthermore, 2 m/l of 0.9% sodium chloride (Ghazi Co., Iran) was administered to participants in the control group. Those in the treatment group received 0.1 mg/kg bodyweight of salbutamol (CIPLA Co. India) combined with 2 m/l of 0.9% sodium chloride. Both administrations were performed using a nebulizer under an oxygen flow of 5-6 l/min for 20 minutes.

Nebulization was given 12 hours after birth for the first time. The vital signs, clinical TTN score (based on expiratory grunting, supraclavicular retractions, subcostal retractions, cyanosis, and nasal flaring) (ranging between 0 and 3 as shown in Table 1), and respiratory frequency were assessed 0.5, 1, and 4 hours after the intervention.[3] All data were recorded in a checklist.

Respiratory support was initiated at the predetermined time using respiratory protection approaches, including no oxygen, intra-incubator oxygen (30%), headbox (40%), a nasal cannula (NC; 50% or 5 liters/minute), and nasal continuous positive airway pressure (NCPAP; 50-60% with 5 cm H_2O). These items were determined based on the neonatal conditions. All the participants were visited and monitored daily before and after the intervention for measuring and recording the intended variables.

Table 1. Clinical scorring of TTN

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

Nasal flaring	None	Mild	Moderate	Severe

Statistical Analysis

SPSS Statistics (version 16, Chicago, USA) was used to analyze the collected data and perform statistical tests. The student's t-test or Mann-Whitney U test was employed to compare the newborns before and after the intervention. The repeated measures analysis of variance (ANOVA) was also used to compare the mean TTN score with the pre- and post-intervention respiratory frequency, the fraction of inspired oxygen (FiO_2), and oxygen saturation level. The significance level was decided to be p-value<0.05.

Ethical considerations

The study protocol was approved by the Ethics Committee of Hamadan University of Medical Sciences, Iran (No. IR.UMSHA.REC.1396.531). In addition, the parents of newborns were fully briefed on the research objectives, procedures, and techniques, and they were assured that their newborns' information would be kept confidential. An informed consent form was also obtained from the parents of newborns. It is also noteworthy that this study was registered at the Iranian Registry for Clinical Trials (Code: IRCT201711139014N201).

Results

This study was conducted on 52 newborns with TTN who were randomly assigned to treatment and control groups. There was no statistically significant difference between the two groups in terms of gender, gestational age, birth weight, maternal diseases, delivery type, and the first- and fifth-minute Apgar score. (Table 2)

Table 3 shows the results of comparing the two groups regarding TTN score, respiratory frequency, oxygen saturation, FiO_2, and SPO_2/FIO_2 ratio. The results indicated that there was no statistically significant difference between the two groups before the intervention (P>0.05). Moreover, no statistically significant difference was found between the groups in the above-mentioned variables half an hour after the intervention, except for the oxygen saturation that was significantly higher in the treatment group (P<0.01). The results also

demonstrated that the mean TTN score, respiratory frequency, and FiO_2 were significantly lower and oxygen saturation and SPO_2/FIO_2 ratio were significantly higher in the treatment group 1 and 4 hours after the intervention ($P<0.05$).

Table 4 summarizes other clinical parameters. No adverse effect was observed in neither of the treatment and control groups.

The repeated measure ANOVA was employed to compare the treatment and control groups in the means TTN score, respiratory frequencies, O_2 saturation, and FiO_2 at different times. The ANOVA test results revealed a significant difference between the two groups in the TTN score ($P=0.03$, Fig.1), respiratory frequencies ($P<0.04$, Fig. 2), O_2 saturation ($P<0.001$, Fig. 3), and FiO_2 ($P=0.03$, Fig. 4).

Discussion

TTN is a significant diagnosis with a treatment dilemma in the NICU. Although the precise pathology of the condition is unknown, it is most commonly caused by delayed reabsorption of intrapulmonary fluid.[11] The mechanism of pulmonary fluid transepithelial movement is described based on adrenergic stimulation at birth. The amiloride-sensitive ENaC-mediated alveolar fluid is stimulated by cyclic adenosine monophosphate and $Ca2^+$.[12,13] The transport of pulmonary fluid into the pulmonary circulation is caused by the movement of Na^+ through the interstitium.[12] In newborns with TTN, pulmonary fluid resorption is delayed. The presence of excess pulmonary water in this clinical syndrome contributes to a decrease in pulmonary compliance. Tachypnea and increased work of breathing compensate for it. The beta-2 agonist's therapeutic role in the treatment of pulmonary edema is to speed up the secretion of excess fluid from the alveolar space. It is accomplished by increasing the function of epithelial transporter proteins. The fluid restriction could be beneficial in the treatment of newborns with severe TTN.[14]

Based on these findings, we hypothesized that salbutamol stimulates lung fluid reabsorption in newborns with TTN, and we investigated the effects of inhaled salbutamol on the clinical outcomes of such newborns.

The study results indicated that inhaled salbutamol reduced the duration of symptoms and respiratory support in newborns with TTN

Consistent with the findings of this study, several studies have confirmed the effect of inhaled salbutamol on the TTN clinical score.[15-19] Similar to Armangil *et al*.[3], we employed

the Rawlins and Smith criteria to evaluate the TTN score. Nevertheless, the post-intervention TTN score in this study was smaller than the score reported by the above-mentioned study. This discrepancy can be attributed to the differences in the drug dosages. Moreover, salbutamol was administered to participants based on their body weight in this study, whereas they administered a constant dose for all participants.

The most important complication of TTN is tachypnea, which occurs 1–2 hours after delivery and can be severe, reaching 60–120 BPM. Prolonged tachypnea can cause a delay in starting enteral feeding, an increase in LOS, and unnecessary antibiotic administration.[9] Kim *et al*. demonstrated that the administration of salbutamol after lung surgery resolved pulmonary edema and improved blood oxygenation in high-risk participants.[11] Ex-vivo evidence obtained from human and animal models indicates that exogenous β2AA stimulates pulmonary fluid absorption.[10,20] Salbutamol, as a β2AA, can increase pulmonary fluid absorption. The study findings, as well as evidence from related studies, demonstrated that β2AA was an effective treatment option for TTN management.[3,11,18,19] It can help to lessen the severity of tachypnea over time.

This study showed that the FiO_2 decreased and O_2 saturation increased over time in the treatment group, which is consistent with the findings of some previous studies.[16,18,21] The duration and demand for respiratory support were significantly lower in the treatment group than in the control group in this study. This is consistent with the finding of other similar studies.[19,22-24]

The study results indicated no significant difference between the two groups in LOS, which is consistent with the findings of a similar study by Kim *et al*.[11] However, most studies have shown that salbutamol reduces LOS.[18,19] This difference can be attributed to neonatal conditions or other confounding variables, such as the male gender[17,25] and route of delivery.[26] This study was focused on minimizing the effects of these intervening variables by matching the groups. It is critical to have therapeutic options available to reduce LOS. However, More comprehensive studies are needed before prescribing inhaled β2AA as a routine treatment for TTN.[27]

Serious bronchospasm, arrhythmia, hypokalemia, and hyperglycemia caused by glycogenolysis have rarely been reported as adverse effects of salbutamol.[28,29] It should be noted that no adverse effect was observed after the administration of salbutamol, which has been confirmed by some similar studies.[17,19,25] Although some other studies have reported

contradictory findings,[19] salbutamol inhalation is believed to be a low-risk treatment for TTN.

Limitations

The small sample size and the lack of other treatment methods were the main limitations of this study. As a result, it is recommended that more comprehensive studies be conducted to confirm the efficacy of inhaled salbutamol as a therapeutic intervention in TTN patients. This study represented a method for gaining new insights into the efficacy of salbutamol in combination with sodium chloride. Instead of using fixed doses, this method proposes administering doses based on the patient's body weight to increase oxygen saturation and lower the TTN clinical score.

Conclusion

The study findings suggested that inhaled salbutamol significantly decreased the TTN clinical score, respiratory frequency, FIO_2, and duration of respiratory support, whereas there was no significant difference between the two groups in terms of LOS and time of enteral feeding. Therefore, a combination of inhaled salbutamol and routine care is recommended to be prescribed for newborns with TTN to improve respiratory distresses and their clinical consequences.

Conflict of interest:

The authors declare that they had no conflict of interest related to newborns with TTN.

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Quick Look

Current knowledge

Although salbutamol may reduce LOS, it is not known that whether it can reduce the need for oxygen therapy and the duration of tachypnea.

What this paper contributes to our knowledge

The results showed an increase in oxygen saturation and a decrease in the TTN clinical score.

In addition, the duration of respiratory support was specified after the administration of salbutamol. This finding suggested that β2AA could be an effective treatment option for TTN.

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Table 2. Comparison of demographic variables between two groups

Variables		Treatment group	Control group	P-value
Gender	Male	46.2	57.7	0.57
	Female	53.8	42.3	
Gestational age		36.31±1.87	36.58±1.47	0.56
Birth weight		2873.69±580.37	2772±469.74	0.66
Apgar score 1st, min		7.92±0.69	8.11±0.59	0.283
Apgar score 5th, min		8.96±0.66	9.11±0.59	0.381
Mode of delivery	Cesarean section	38.5	57.7	0.16
	Normal vaginal delivery	68.5	42.3	
Maternal disease	Yes	30.8	34.6	0.76
	No	39.2	65.4	
Type of respiratory support	No oxygen	0	0	0.53
	Intra-incubator oxygen	3.8	15.4	
	Hood	42.3	38.5	
	NC*	26.9	26.9	
	NCPAP**	26.9	19.2	

*Nasal cannula

** Nasal continuous positive airway pressure

Table 3. Comparison of clinical parameters between two groups

Variable		Treatment group	Control group	P-value
TTN score	Before treatment	2.08±0.85	2.00±0.69	0.797
	0.5 hours after the intervention	1.54±0.90	1.34±0.56	0.655
	1 hour after the intervention	0.73±0.78	1.27±0.60	0.005
	4 hours after the intervention	0.0±0.0	0.88±0.59	<0.001
Respiratory frequency	Before treatment	76.23±6.08	77.46±6.87	0.49
	0.5 hours after the intervention	72.27±5.27	74.88±6.14	0.106
	1 hour after the intervention	68.81±3.79	74.31±6.14	<0.005

	4 hours after the intervention	64.81±2.84	68.59±5.99	<0.005
O2 saturation, %	Before treatment	91.42±1.53	91.24±1.63	0.66
	0.5 hours after the intervention	92.34±1.49	91.23±1.53	0.01
	1 hour after the intervention	93.73±1.8	92.65±1.32	0.01
	4 hours after the intervention	95.34±1.06	92.53±1.3	<0.005
FiO_2, %	Before treatment	64.74±8.59	62.50±8.86	0.977
	0.5 hours after the intervention	58.41±7.58	61.74±8.59	0.152
	1 hour after the intervention	53.27±6.63	57.69±7.51	0.022
	4 hours after the intervention	45.38±7.20	56.34±7.69	<0.001
SPO_2/FIO_2 ratio	0.5 hours after the intervention	159.01±23.31	151.13±24.75	0.243
	1 hour after the intervention	176.07±23.23	161.07±24.00	0.026
	4 hours after the intervention	206.11±48.83	167.40±23.09	<0.001

Table 4. Comparison of outcomes between two groups

Variables (Day)	Treatment group	Control group	P-value
Duration of respiratory support	2.42±0.7	3.15±0.83	0.002
Length of hospital stay	6.31±1.05	5.77±1.11	0.078
Duration of antibiotic therapy	5.46±1.14	5.23±1.24	0.48
Time to start oral feeding	2.35±0.48	2.27±0.45	0.55
Maximum oral feeding time	4.31±0.55	4.19±0.57	0.46

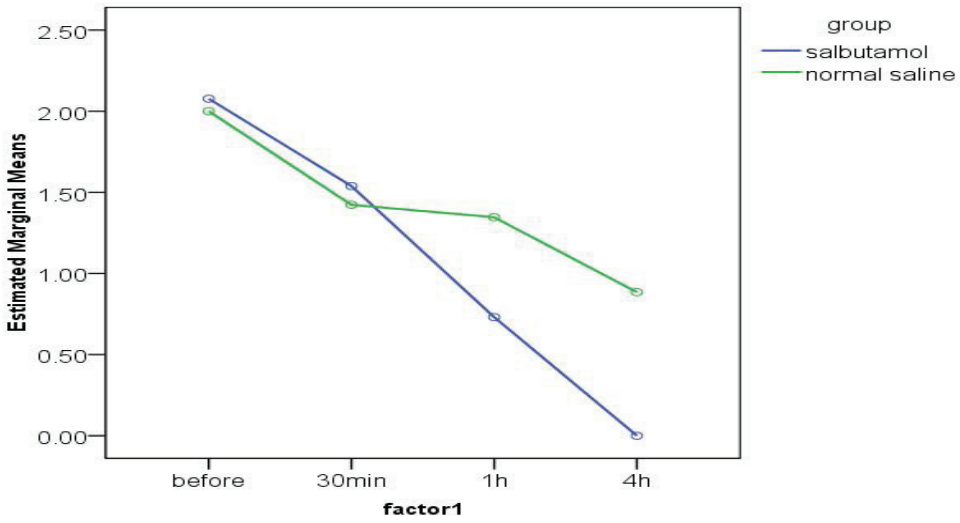

Figure 1. The means of TTN Score in treatment and control groups at different time periods

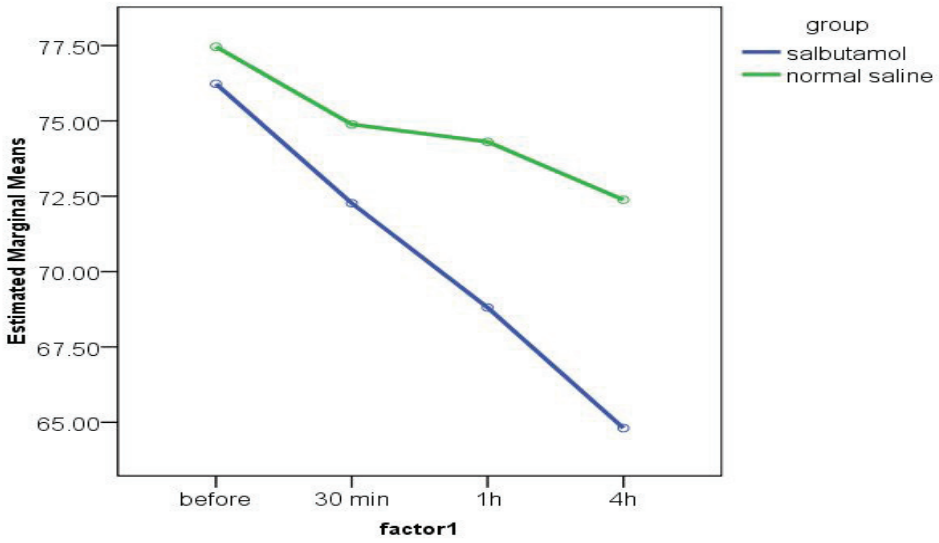

Figure 2. The means of respiratory frequency in treatment and control groups at different time periods

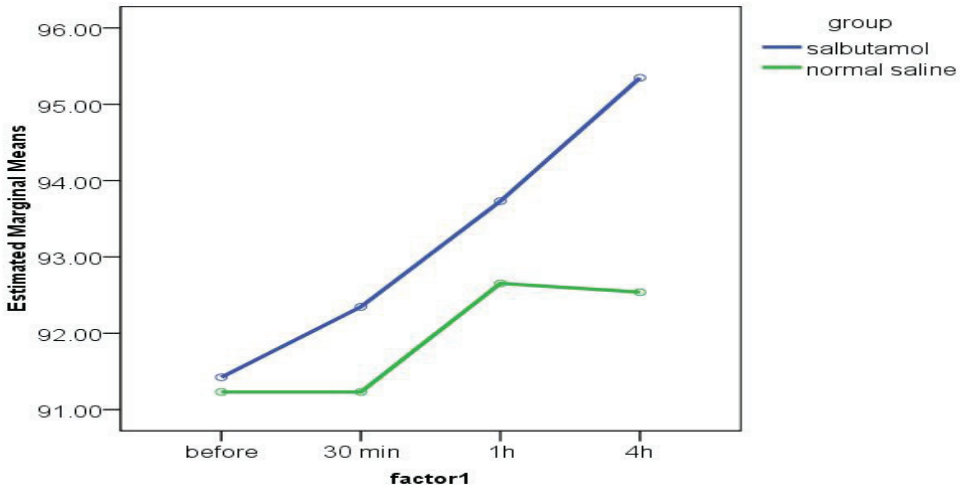

Figure 3. The means O2 saturation in treatment and control groups at different time periods

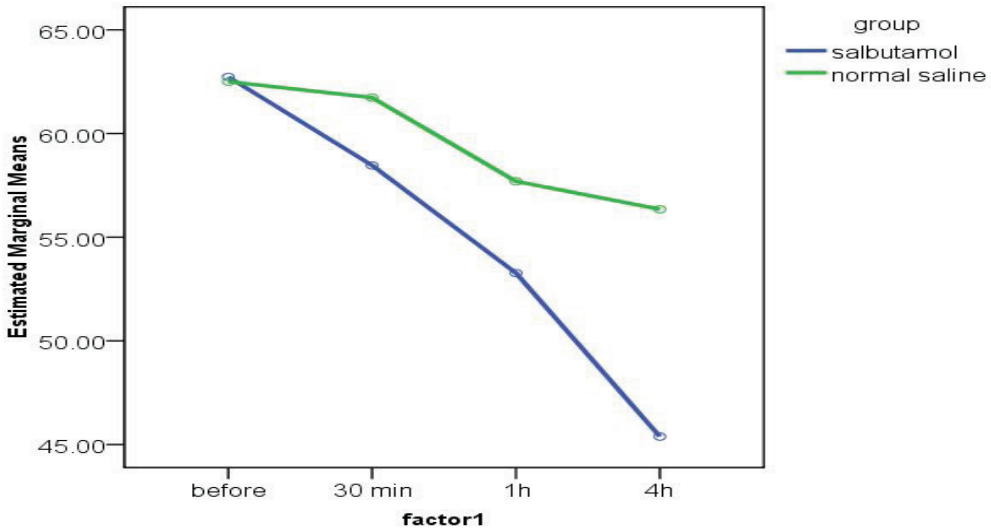

Figure 4. The means FiO2 in treatment and control groups at different time periods

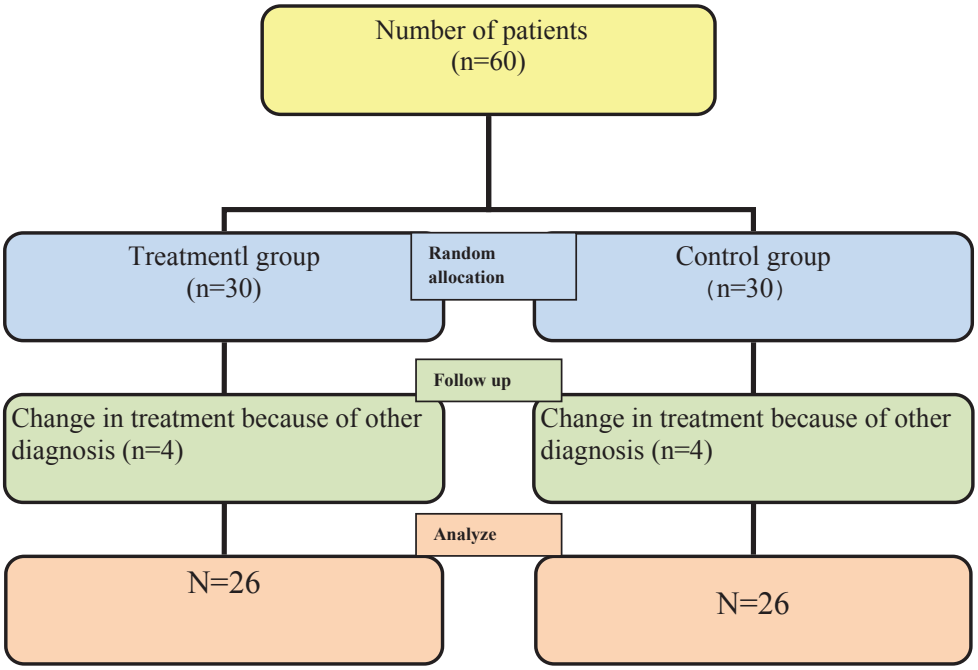

Diagram 1. Sample selection process