DOES COMBINING INHALED SALBUTAMOL WITH INTRAVENOUS CORTICOSTEROIDS PREVENT INTUBATION PROVOKED BRONCHOCONSTRICTION? A RANDOMIZED TRIAL.

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Abstract

Background

Endotracheal intubation may induce serious bronchoconstriction in patients with bronchial hyper-reactivity. Although intravenous corticosteroids are used in combination with $\beta 2$ agonists in the active management of bronchoconstriction, their prophylactic role is still not well defined. The aim of this study is to compare between inhaled salbutamol alone, salbutamol + intravenous hydrocortisone and salbutamol + intravenous methylprednisolone combinations in preventing endotracheal intubation provoked bronchoconstriction in patients with airflow obstruction undergoing diagnostic laparoscopic gynecological procedures.

Materials and methods

The study was carried on 45 patients with obstructive airway disease scheduled for diagnostic laparoscopic gynecological procedures. Patients with FEV1 <80% of predicted and FEV1/FVC < 0.7 were included in the study. Patients were randomized using computer generated random numbers into three groups, 15 patients in each group. *Group 1*: patients received 0.2 mg salbutamol through a meter dose inhaler 10 minutes before intubation. *Group 2*: In addition to salbutamol, patients received two doses of intravenous hydrocortisone 1mg/kg 6 hours and 1 hour before intubation. *Group 3*: In addition to salbutamol, patients received two doses of intravenous methylprednisolone 1mg/kg 6 hours and 1 hour before intubation.

Results

In group 1 (salbutamol), 7/15 patients (46.66%) developed wheezing after tracheal intubation compared to 6/15 patients (40%) in group 2 (salbutamol/hydrocortisone) (P=0.71). Wheezing developed in 1/15 patients (6.66%) in group 3 (salbutamol/methylprednisolone) which was significantly lower when compared to groups 1 (P=0.013) and 2 (P=0.03). There were no significant changes between groups as regards peak airway pressures, mean blood pressure and blood glucose levels.

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Conclusion

Combining inhaled salbutamol with intravenous methylprednisolone resulted in significantly less intubation provoked bronchoconstriction compared to salbutamol alone and salbutamol combined with hydrocortisone.

Introduction

Endotracheal intubation may trigger bronchospasm. This may result in life threatening ventilation-perfusion mismatch and hypoxia[1]. Patients with obstructive airway disease have hyper-reactive airways, thus, post-intubation bronchospasm is more likely in this group of patients[2-4].

Bronchial smooth muscle tone is under control of the parasympathetic nervous system that also regulates inflammatory and allergic airway responses. Following endotracheal intubation, postganglionic cholinergic fibers release acetylcholine that binds to bronchial M3 and M2 muscarinic receptors causing smooth muscle contraction and inhibiting β2 mediated smooth muscle relaxation respectively[5].

Unfortunately in patients with obstructive airway disease, the cholinergic input may be increased or dysregulated resulting in airway hyper-reactivity and making these patients more liable to intubation induced bronchoconstriction. Moreover, the non-cholinergic non-adrenergic (NCNA) innervation that results in bronchial smooth muscle relaxation via the release of nitric oxide is suppressed in such patients[6].

Systemic steroids remain a mainstay of the treatment of acute bronchospasm. Intravenous corticosteroids have long been used in combination with inhaled $\beta 2$ agonists in the active management of bronchoconstriction[7]. However, the prophylactic role of this combination in preventing post-intubation bronchoconstriction is still not well defined.

The aim of this study was to compare inhaled salbutamol alone, inhaled salbutamol + IV hydrocortisone and inhaled salbutamol + IV methylprednisolone combinations in preventing endotracheal intubation provoked bronchoconstriction in female patients with obstructive airway disease undergoing diagnostic laparoscopic gynecological procedures.

Patients and Methods

After obtaining approval from the ethical committee and informed patient consent, this prospective randomized double blinded study was carried in Ain Shams University Obstetrics and Gynecology hospital in the time period from January 2015 to January 2018 on 45 patients with obstructive airway disease scheduled for diagnostic laparoscopic gynecological procedures.

Spirometry was performed for patients with history suggestive of hyper-reactive airways (as cough, dyspnea and wheezing in response to various stimuli) who had no history of steroid intake and not receiving bronchodilators for at least one month before. Patients with FEV1 <80% of predicted value and FEV1/FVC < 0.7 were included in the study.

Exclusion criteria included smoking, other respiratory disorders and patients with active wheezing at time of preoperative assessment. Patients with history of diabetes, hypertension or cardiac disease were also excluded from the study.

Randomization

Patients were randomized using computer generated random numbers into three groups, 15 patients in each group. *Group 1*: patients received salbutamol through a meter dose inhaler (two puffs equivalent to 0.2 mg) 10 minutes before intubation. *Group 2*: In addition to salbutamol, patients received two doses of intravenous hydrocortisone 1mg/kg 6 hours and 1 hour before intubation. *Group 3*: In addition to salbutamol, patients received two doses of intravenous methylprednisolone 1mg/kg 6 hours and 1 hour before intubation.

Intubation was performed by an anesthesiologist with at least three years of experience. The primary outcome was the incidence of post-intubation wheezing. Wheezing was assessed independently by the two most senior anesthesiologists in the operating theatre. Both anesthesiologists were asked to auscultate

the lungs bilaterally at baseline and 2 minutes post-intubation at the mid-axillary, mid-clavicular and parasternal lines. Wheezing was defined as high pitched expiratory rhonchi[8] that were audible at any of the auscultation sites. Detection of audible wheezes by both anesthesiologists was necessary before confirming the presence of wheezes. Anesthesiologists performing intubation and auscultation were blinded to the study group.

Secondary outcomes included peak airway pressures displayed by the anesthesia ventilator: recorded 1 minute, 5 minutes and 10 minutes post-intubation, blood glucose and mean blood pressure levels recorded before induction of anesthesia then 30, 60 and 120 minutes after induction of anesthesia.

Anesthetic technique

Standard monitors (ECG, pulse oximetry, capnography, non-invasive blood pressure) were applied to all patients. In all patients anesthesia was induced with propofol (1.5 mg/kg), fentanyl (2 μg/kg) and rocuronium (0.6mg/kg) followed by endotracheal intubation with a 7.5 internal diameter cuffed endotracheal tube. Anesthesia was maintained with sevoflurane in 100% oxygen. All patients were

Fig. 1
CONSORT Flow Diagram

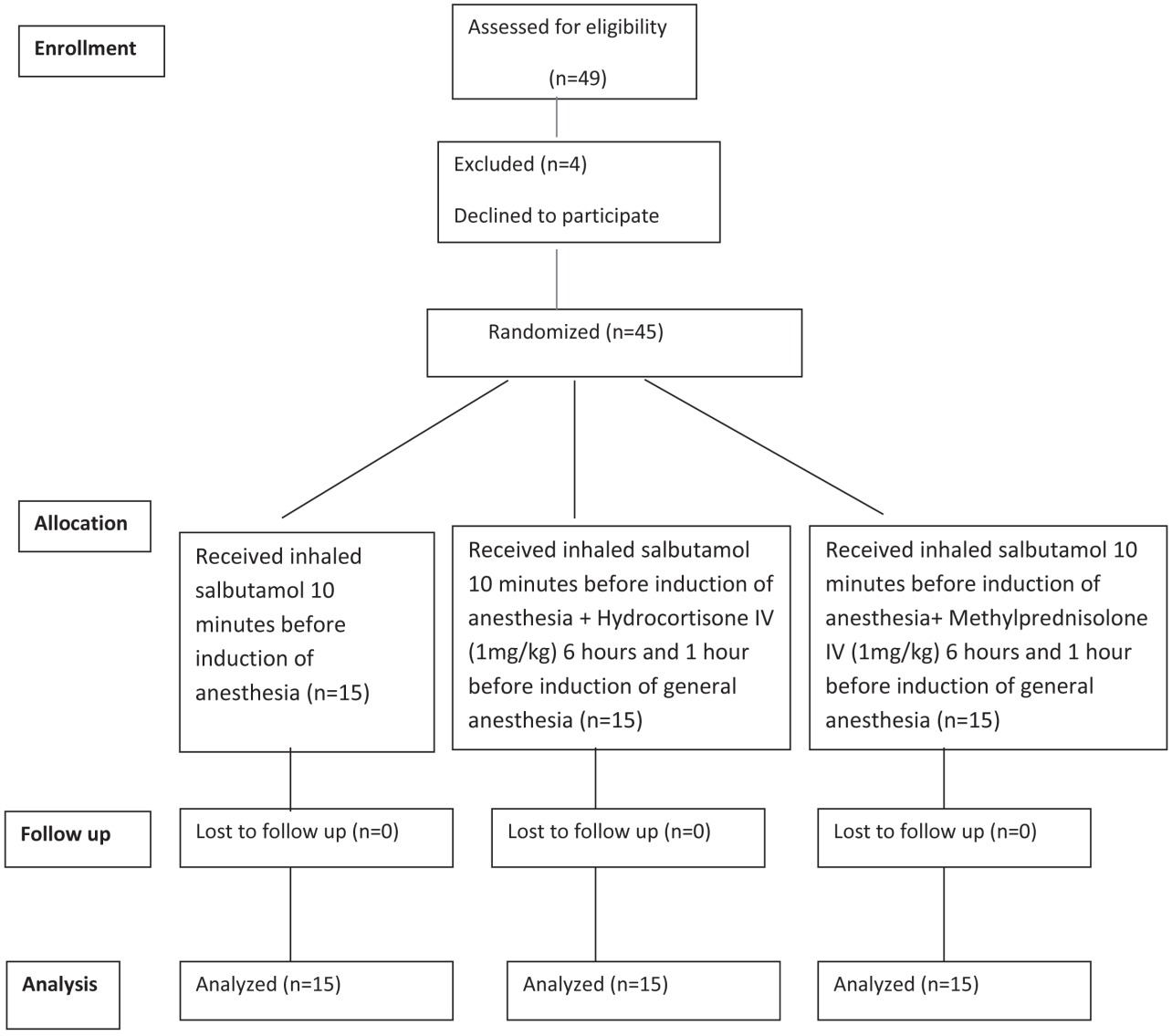


Table 1
Demographic data and baseline FEV1

	Salbutamol (n=15)	Salbutamol/hydrocortisone (n=15)	Salbutamol/Methyl-prednisolone (n=15)	P-value
Age (y)	23(6.8)	27.2(5)	27(4.4)	0.073
Weight (kg)	75.9 (10.2)	75.2 (9.5)	81.5(6.9)	0.121
Height (m)	1.7 (0.05)	1.69(0.06)	1.73 (0.05)	0.116
FEV1(% predicted)	74.1 (3)	73.2 (2.6)	71.4 (4.2)	0.09

(FEV1: Forced expiratory volume in first second) Data presented as mean (SD).

mechanically ventilated with tidal volumes of 8 ml/kg at a rate of 12 breaths/min and I:E ratios of 1:2.5. Any anesthetic agents that are accused for triggering bronchospasm (as morhine. Pethidine and atracurium) were avoided,

Patients developing post-intubation wheezing were treated by deepening the anesthesia with propofol and/or increasing the concentration of sevoflurane together with the administration of 4 additional puffs of salbutamol (0.4mg) delivered by a meter dosed inhaler through the endotracheal tube. An additional dose of hydrocortisone 2mg/kg was given to patients not responding to inhaled salbutamol. None of the patients required further management.

Sample size calculation

In the work of Silvanus et al[9], 12.5% of the patients in the methylprednisolone group developed wheezing compared to 77% in the salbutamol group. Guided by the aforementioned data, the sample size was calculated based on study power of 90% (β error of 0.1) and type I α error of 0.05. The calculated sample size was 15 in each group.

Statistical Analysis

SPSS statistics (V.210.0, IBM Corp., USA 2012) was used for data analysis. Categorical data (percentage of patients developing post intubation wheezing) was analyzed using Chi-square test. Numerical data was analyzed using one way analysis of variance (ANOVA). Student t test was used as the post-hoc test if significance was reached. P-value <0.05 was considered statistically significant.

Results

Demographic data and baseline Forced Expiratory Volume in first second (FEV1) were comparable between the three groups (Table 1).

Incidence of wheezing

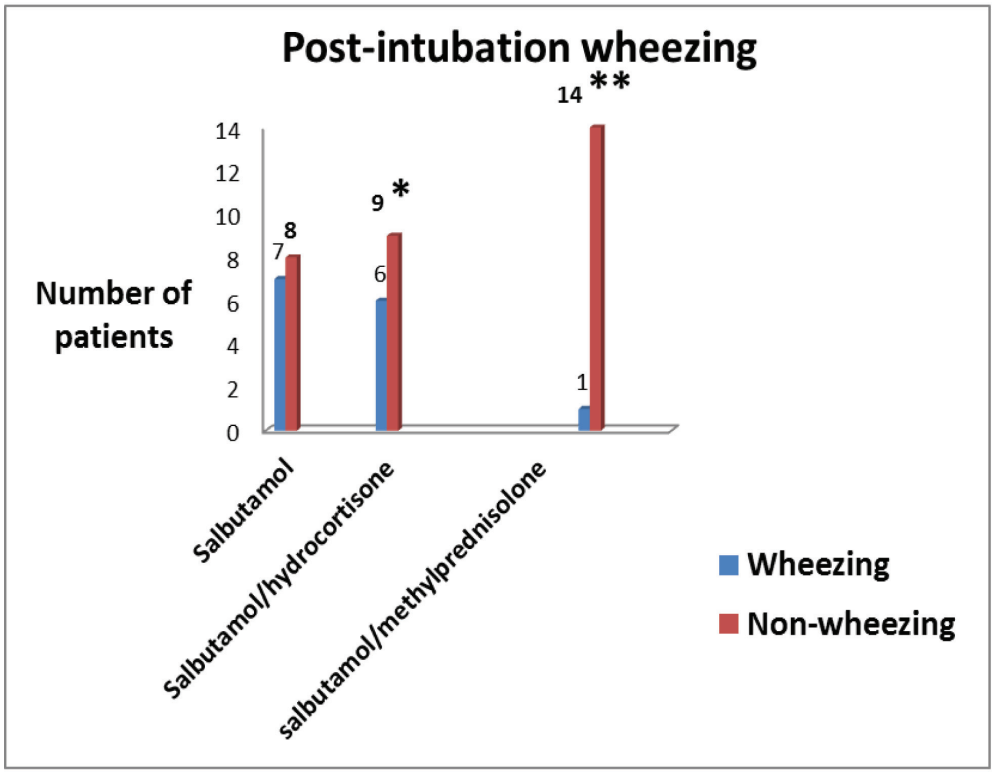
In group 1 (salbutamol), 7/15 patients (46.66%) developed wheezing after tracheal intubation compared to 6/15 patients (40%) in group 2 (salbutamol/hydrocortisone) (P=0.71).

Wheezing developed in 1/15 patients (6.66%) in group 3 (salbutamol/methylprednisolone) which was significantly lower when compared to groups 1 (P=0.013) and 2 (P=0.03) (Figure 2).

In regard to peak airway pressures there were no significant differences among the three groups at 1, 5 and 10 minutes post-intubation (Figure 3).

There were no significant differences among the three groups as regards blood glucose and mean blood pressure levels at each of the following time intervals: T1 (before induction of anesthesia), T2, T3, T4 (30, 60 and 120 minutes after induction of anesthesia respectively) (Tables 2 and 3).

Fig. 2
Incidence of post-intubation wheezing



* P<0.05 (salbutamol/methylprednisolone group vs salbutamol group)
** P<0.05 (salbutamol/methylprednisolone group vs salbutamol/hydrocortisone group).

Fig. 3
Peak airway pressures (cmH2O) at 1,5 and 10 minutes after intubation. (Mean + SD)

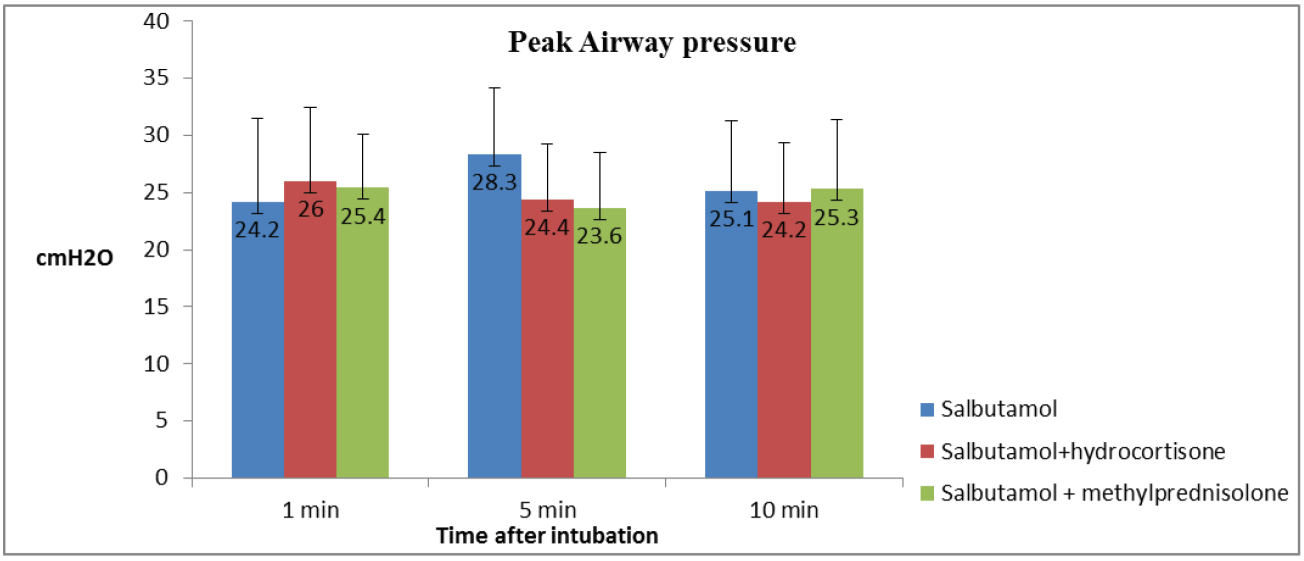


Table 2
Mean Blood glucose levels

	Salbutamol (n=15)	Salbutamol/hydrocortisone (n=15)	Salbutamol/Methyl-prednisolone (n=15)	P-value
T1	160.6 (16.5)	178.2 (25.5)	182 (30.8)	0.054
T2	188.4 (20.2)	172.2 (34.6)	190.3 (22.8)	0.136
T3	195.1 (19.4)	184.6 (23.8)	200.4 (20.2)	0.129
T4	192.4 (17.4)	198.2 (22.5)	205.5 (20.6)	0.22

Blood glucose levels (mg/dL) at the following time intervals: T1= before induction of anesthesia, T2=30 minutes after induction of anesthesia, T3= 60 minutes after induction of anesthesia, T4= 120 minutes after induction of anesthesia. Data presented as mean (SD).

Table 3
Mean Blood Pressure (MBP)

	Salbutamol (n=15)	Salbutamol/hydrocortisone (n=15)	Salbutamol/Methyl-prednisolone (n=15)	P-value
T1	76.8(8.8)	74.2(8.6)	70(8.4)	0.10
T2	78.8(8.4)	82.4(11.8)	80.9 (9.2)	0.61
T3	84.8 (6.2)	84.4 (7.8)	85.5(8.3)	0.92
T4	82.5(7.8)	85.2(11.7)	86.6(7.2)	0.46

Mean blood pressure levels (mmHg) at the following time intervals: T1= before induction of anesthesia, T2=30 minutes after induction of anesthesia, T3= 60 minutes after induction of anesthesia, T4= 120 minutes after induction of anesthesia. Data presented as mean (SD).

Discussion

The current study showed that combining inhaled salbutamol with intravenous methylprednisolone resulted in significantly less intubation provoked bronchoconstriction compared to salbutamol alone and salbutamol combined with intravenous hydrocortisone in patients with obstructive airway disease undergoing diagnostic gynecological laparoscopic procedures.

Methylprednisolone has five times the anti-inflammatory potency of hydrocortisone, with less mineralocorticoid properties. Concentrations in lung parenchyma are higher after the administration of methylprednisolone compared to hydrocortisone[10]. The plasma half-life of methylprednisolone is 180 minutes. Hydrocortisone has equal glucocorticoid and mineralocorticoid properties with a plasma half-life of 90 minutes. The *bronchial effects* of intravenous steroids are not immediate and may not be seen for 4 to 6 hours after initial administration[11]. For this reason, the pre-induction dose of corticosteroids administered in this study was preceded by a similar dose 6 hours before.

There are no published recommendations concerning prophylactic doses of intravenous steroids in the prevention of intubation induced bronchospasm. A dose response relationship for corticosteroids has not been identified either. Supported by the results of previous studies that found no difference in outcome between high and low dose corticosteroid doses in asthma, minimal corticosteroid doses were used in the current study aiming to minimize adverse effects. Weight based doses were used rather than fixed doses (1mg/kg IV for each of methylprednisolone

and hydrocortisone). *Marquette et al*[12] found intravenous methylprednisolone doses of 1 and 6mg/kg to be comparable in acute severe asthma. The study carried by *Bowler and his colleagues*[13] revealed that hydrocortisone 50 mg intravenously four times daily for two days followed by low dose oral prednisone was as effective as 200 or 500 mg of hydrocortisone followed by higher doses of prednisone in severe asthma.

Previous studies have shown preoperative $\beta 2$ agonists to be effective in the prevention of intubation induced bronchoconstriction. The study carried by *Maslow and his coworkers*[14] showed that inhaled albuterol was effective in reducing airway responsiveness to endotracheal intubation under general anesthesia in asthmatic patients. *Groeben et al*[15] came to a conclusion that combined treatment with lidocaine and salbutamol can be recommended for awake intubation in asthmatic patients. However, bronchospasm associated with obstructive lung disease is also related to airway inflammation[16], thus, making the preventive and therapeutic role of $\beta 2$ agonists as a sole agent in such condition questionable.

In addition to reversing mucosal edema, decreasing vascular permeability and inhibiting the release of inflammatory mediators[17], corticosteroids can enhance the bronchodilator effects of β^2-adrenergic receptor agonists by increasing the number of β^2-receptors[18].

The role of systemic corticosteroids in the prophylaxis of bronchoconstriction evoked by instrumentation of hyper-reactive airways has not been extensively studied and studies in this field remain scarce.

Sylvanus and his colleagues[9] carried a study on the effect of combining β_2 agonists with oral corticosteroids for the prevention of post-intubation bronchospasm. The administration of oral methylprednisolone (40 mg orally) for 5 days together with inhaled salbutamol improved the lung functions and decreased the incidence of wheezing after tracheal intubation.

Other studies focused on the role of systemic steroids in preventing perioperative bronchospasm.

Kabalin and his co-workers[19] carried a study to determine the incidence of perioperative complications in 89 asthmatic patients who received preoperative treatment with systemic corticosteroids. Patients received prednisone 1mg/kg for 3-7 days preoperatively along with hydrocortisone 100mg/8h perioperatively. Only 4.5% of patients developed mild postoperative bronchospasm; while 5.6% developed postoperative infections of which 2.2%were wound infections.

In the work of *Matsuse et al*[20], patients with mild asthma undergoing surgery under general anesthesia with endotracheal intubation were treated with corticosteroids during the perioperative period, consisting of a course of oral prednisolone 10-20 mg/day for 1-2 days pre-operatively, methylprednisolone 80-125 mg 2 h before the operation, followed by 80 mg methylprednisolone just after the operation. The incidence of perioperative bronchospasm was evaluated based on medical records. Only 4% of patients developed mild asthma during the perioperative period. The use of the same therapeutic regimen in another six asthmatics significantly suppressed airway hyper-responsiveness to inhaled methacholine.

Conclusion

The current study revealed that combining inhaled salbutamol with intravenous methylprednisolone resulted in significantly less intubation provoked bronchoconstriction compared to salbutamol alone and salbutamol combined with intravenous hydrocortisone.

More studies are still needed to assess long term outcomes and patients that will benefit from preoperative steroid therapy.

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