Effects of oral methylprednisolone and inhaled salbutamol in the decrease of wheezing in patients with asthma after tracheal intubation

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ABSTRACT

Background: Airway instrumentation in patients with bronchial hyperreactivity, may evoke life-threatening asthma attack and a good strategy for the prevention of bronchospasm has not been defined. In a randomized, prospective, placebo-controlled study, it was determined whether prophylaxis with either inhaled salbutamol—or combined inhaled salbutamol and oral methylprednisolone improves lung functions and prevents wheezing after intubation.

Methods: Thirty one patients with partially reversible airway obstruction (airway resistance> 180%, forced expiratory volume in 1 second [FEV1] < 70% of predicted value, and FEV1 increase> 12% after two puffs of salbutamol) were randomized to receive daily either 3-2 puffs (0.2 mg) of salbutamol (n =16) or 3-2 puffs (0.2 mg) of salbutamol and 40 mg of methylprednisolone (n = 15) orally for 5 days. In all patients lung function was evaluated daily and wheezing changes was assessed before and 5 minutes after tracheal intubation.

Results: Both salbutamol and combined inhaled salbutamol and oral methylprednisolone treatment significantly improved airway resistance and FEV1 to a steady state, with no difference between groups. When a single-dose of salbutamol pre-induction or prolonged salbutamol treatment was employed, most patients (8 of 10 and 7 of 9) experienced wheezing after intubation. In contrast, only one patient of those who received both salbutamol and methylprednisolone experienced wheezing (P = 0.0058).

Conclusions: Pretreatment with either salbutamol or combined inhaled salbutamol and oral methylprednisolone significantly improves lung function and decreases the incidence of wheezing after tracheal intubation. Methylprednisolone decreases incidence of wheezing more than salbutamol. Therefore, in patients with bronchial hyper reactivity, preoperative treatment with both methylprednisolone and salbutamol minimizes intubation-evoked broncho-constriction.

Keyword: Salbutamol**,** methylprednisolone**,** tracheal intubation

INTRODUCTION

In patients with bronchial hyperactivity tracheal intubation may evokes life- threatening bronch-ospasm which may leads to perioperative complications requiring intensive care treatment. Bronchospasm is especially possible in patients with active signs of obstructive airway disease (1). Treatment of previously-undiagnosed bronchial hyperactivity before tracheal intubation seems to be an important initiative to improve lung function and to mitigate bronchoconstriction. While results of several studies have suggested that patients with chronic obstructive pulmonary disease or asthma can benefit from preoperative treatment (2-4) the length of treatment and the necessity of the use of systemic corticosteroids are unknown and there is no evidence showing that preoperative therapy improves lung function and is associated with a lesser risk of bronchospasm after intubation.

This study was conducted to investigate whether a short preoperative course of corticosteroids in addition to inhaled beta agonists improves lung function or, more importantly, diminishes bronchoconstriction after tracheal intubation.

MTERIALS AND METHOD

Methods

After obtaining approval of the local ethics committee and informed written consent, 41 inpatients which were assigned to undergo

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surgery enrolled in this randomized, double-blind, prospective study.

The inclusion criteria were patients with reversible airway obstruction who were either newly diagnosed during the preoperative investigations or were known cases who had received anti-obstructive therapy previously but had not received therapy for at least one month

Airway obstruction was defined as an airway resistance (R_{aw}) greater than 180% of that predicted and a forced expiratory volume in 1 second (FEV1) less than 70% of that predicted. Reveribility or responsiveness of obstruction was indicated by American Thoracic Society (ATS) definition as increase of %12 and 200ml in FEV1 after administration of a bronchodilator. Patients who did not comply with airway obstruction and/or reversibility definitions or received anti-obstructive treatments during last month were excluded.

Study Protocol

To account for potential variability of spirometric measurements, diurnal variation, and environmental influences, lung function tests were always performed at the same time of the day in an air-conditioned room. After initial pulmonary function testing to confirm the presence of reversible bronchoconstriction, patients were randomly allocated to receive in a double-blind fashion a 5-day treatment course of either combined salbutamol [two puffs (0.2 mg) 3 times/day] and methylprednisolone (40 mg orally) or salbutamol and oral placebo. Administration of medications was supervised, and lung function tests were scheduled daily, unless the patients underwent surgery or were discharged without surgery for other reasons. Another 10 patients, serving as a control group, did not undergo any prolonged pretreatment and only received two physician- guided puffs of salbutamol before induction of general anesthesia on the day of surgery. Seven patients receiving salbutamol and seven patients both receiving salbutamol methylprednisolone treatment did not complete the full 5-day pretreatment for clinical reasons (discharge or more urgent surgery), but all underwent pretreatment and lung function tests for at least 3 days. Accordingly, the effects of intubation on the incidence of wheezing in these patients were not investigated. Induction of anesthesia was standardized using fentanyl (1.5 g/kg), thiopental (5 mg/kg), and vecuronium (0.1 mg/kg), and auscultation for wheezing was performed before and 5 minutes after tracheal intubation by an assessor blinded to the specific treatment.

Assays

Lung function was measured using a body plethysmograph with an integrated spirometer (Jaeger, Würzburg, Germany) by a single, trained person. Initially, vital capacity (VC), FEV1, and R_{aw} were assessed at baseline. When lung function testing revealed evidence of airway obstruction, the presence of reversible bronchoconstnction was confirmed in each patient by an increase in FEV1 of more than 10% after administration of two puffs (0.2 mg) of salbutamol. To assess bronchoconstriction in response to intubation, auscultation was always performed on either side of the chest at the fourth intercostal space (ICS) in the midaxillary line, the fifth ICS in the midclavicular line, and the second ICS in the parasternal line before intubation and anesthesia and 5 minutes after intubation. The presence of wheezing was determined by a simple yes or no score by a physician not involved in this study and blinded to the protocol. All patients were mechanically ventilated 10 times/min with a tidal volume of 10 ml/kg body weight and with an inspiratory flow of 40 l/mm. Wheezing was defined as high pitched continuous sound lasting more than 250msec that were audible at at least three of six auscultation sites.

Statistical Analysis

Data are presented as mean ± SD. Hypotheses were tested by two-way repeated-measurement analysis of variance followed by post hoc t tests using the Bonferroni correction of the error and the Fisher exact test. A null hypothesis was rejected with an error P value of less than 0.05.

RESULTS

Table 1 summarizes Patients' characteristics. Only 9 patients in the salbutamol group and 8 patients in the combined group could finish the study protocol no patient in any group experienced wheezing before intubation. Lung Functions during salbutamol or salbutamol-corticosteroid treatment are summarized in Table 2. There was no difference in the degree of measured improvement between treatments with combined salbutamol-methylprednisolone and salbutamol alone. Most improvements in R_{aw}, FEV1, and VC of pretreated patients occurred within 1 day, and no further significant effects were detected thereafter. There was a variation between the completion of pre-surgery treatment and the time of surgery which was 1.3 days for the salbutamol group and 1.8 days for the combined group (p=0.087). After tracheal intubation, there was a significant difference in the incidence of wheezing among the tested groups (p = 0.0058).

Table 1. Patients' characteristics.

Variable	Group		P value
	Salbutamol	Combined Salbutamol-Methylprednisolone	
Gender (male)	8 (53%)	10 (66%)	0.87
Age (mean)	53 yr	57 yr	0.43
Pretreatment Vital Capacity (%, mean)*	79%	81%	0.31
Pretreatment FEV1(%, mean)*	68%	66%	0.82
Pretreatment R_{aw} (%, mean)[8]	196%	201%	0.45

*These parameters are expressed as mean percentage compared to a prediceted value.

Table 2. Changes in respiratory indices in the two study groups.

Index	Group		P value
	Salbutamol	Combined Salbutamol-Methylprednisolone	
Increase in FEV1	23%	29%	0.65
Increase in VC	15%	18%	0.42
Decrease in R_{aw}	36%	42%	0.091

Of those patients receiving combined salbutamol-methylprednisolone, only a single patient experienced wheezing after intubation, whereas 7 of 9 patients in the group with prolonged salbutamol pretreatment ($p = 0.0152$) and 8 of 10 patients receiving a single dose of salbutamol pre-induction experienced wheezing ($p = 0.0152$). There was no difference between the prolonged and single-dose in salbutamol groups ($p = 0.99$). Two patients in prolonged salbutamol group and 3 patients in single-dose salbutamol group required additional treatment for bronchospasm. Therefore, wheezing occurred much more frequently in patients receiving salbutamol whether they received a pretreatment course or only a single dose of salbutamol, in comparison with patients who received methylprednisolone.

DISCUSSION

In patients with untreated and partially reversible obstructive airway disease, salbutamol treatment, with or without methylprednisolone, improved lung function significantly within a day. Addition of methylprednisolone to salbutamol pretreatment significantly decreased wheezing after intubation. Reversible airway obstruction has been defined differently by various authors. Although some consider a change of 10% in FEV1 or VC to be clinically relevant (5), others recommend a change of 15% after inhaled beta agonists (6). An important factor in this kind of study is the choice of induction agents which apparently, have an effect on airway resistance. However intravenous administration of fentanil in doses of 20-fold higher than those which was used in this study has resulted in a modest increase in airway resistance (7) and therefore the clinical relevance of this effect in this study can be regarded negligible. Reports the effects of barbiturates on airway resistance are controversial. In the clinical range, administration of thiopental may results in some constriction but at slightly higher doses may even leads to bronchodilation (8, 9). However, these drugs were chosen as induction agents because they do not reduce airway resistance by themselves, and the authors' purpose was to determine the protective ability of preoperative treatment (10). Undoubtedly, inhaled beta-adrenergic agonists can improve airway obstruction and lung function in anesthetized patients with a history of smoking, and a single treatment attenuates the response to intubation (2). However, it has been reported that in volunteers with bronchial hyperreactivity undergoing awake fiber optic intubation under local anesthesia, salbutamol pretreatment did not fully block the response to tracheal lntubation (11).

In anesthetized patients in this study, the incidence of wheezing after intubation was high (80%), despite a prolonged course of inhalational salbutamol pretreatment. It is unlikely that this finding relates to underdosing because all inhalations were observed by a physician. In general, beta-adrenergic agonists can evoke hypokalemia and arrhythmias, which, in high doses, can lead to morbidity and mortality (12, 13). Therefore, with respect to tachycardia, some anesthesiologists hesitate to use beta-adrenergic agonists in elderly patients. However, by the use of salbutamol, through a metered- dose inhaler, and administration of a dose lower than 8 puffs, adverse effects in general are hardly detectable, and major adverse effects are not expected (14,15).

Corticosteroids can enhance the bronchodilatory effect of beta-adrenergic receptor agonists. In addition to the direct effect smooth muscle, they increase the number of beta-adrenergic receptors

and their response to beta-adrenergic receptor agonists (16). However, whether short-term oral corticosteroid administration in addition to a beta-adrenergic receptor agonist can attenuate the response to mechanically evoked airway irritation is not known. Although inhalational steroids are believed to take weeks to months to attain their full effect, systemically administered corticoids may evoke this effect within 48 hours. Accordingly, administration of glucocorticoids in dosages of 0.5-1 mg/kg orally is recommended (17, 18).

In this study, methylprednisolone was chosen because it yields higher lung parenchymal concentrations than cortisol and therefore is a preferred corticosteroid in systemic asthma treatment (18, 19). Some surgeons believe that peri-operative administration of corticosteroids in non adrenal-deficient patients may increase post-operative problems. Such as wound healing and infectious complications. However but there are reports that short course, pre-operative steroid treatment may not be harmful in this regard (17,20). Significant reduction in reflex bronchoconstriction in patients at risk may outweigh potential adverse effects of steroids. Adverse effects may be limited by reduction in total duration of pre-operative steroid treatment, and further investigation is required to determine the shortest time necessary for effective pretreatment of patients with reversible obstructive airway disease.

In conclusion, salbutamol pretreatment for 5 days improves baseline lung function within 1 day, with no further improvement thereafter, but does not mitigate the bronchoconstrictor response to intubation compared with a single treatment just before intubation. Additional administration of methylprednisolone did not augment the effects of salbutamol in improving lung function, but it markedly decreased the incidence of wheezing, hence bronchospasm after tracheal intubation.

REFERENCES

1. Warner DO, Warner MA, Barnes RD, Offord KB, Schroeder DR. Gray FT, Yunginger JW. Preoperative respiratory complications in patients with asthma. Anesthesiology 1996;85:460-7.
2. Kil IJ-k, Rooke GA, Ryan-Dykes MA, Bishop MJ. Effect of prophylactic bronchodilator treatment on lung resistance after tracheal intubation. Anesthesiology 1994;81:43-8.
3. Gracey DR, Divertie MB, Didier EP. Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease. Chets 1979;76:123-9.
4. Groeben H, Silvanus M-T, Beste M, Peters J. Combined intravenous lidocaine and inhaled salbutamol protect against bronchial hyper reactivity more effectively than lidocaine or salbutamol alone. Anesthesiology 1998; 89: 826-8.
5. Bishop MJ, Chenev FW Anesthesia for patients with asthma (editorial) Anesthesiology 1996;85:455-6.
6. Smith HR, Irvin CG, Cherniac RM. The utility of spirometry in the diagnosis of reversible airway obstruction. Chest 1992;101:1577-81.
7. Neto PPR, Auler JOC Jr. Respirators mechanical properties during fentanyl and ulfentanil anesthesia. Can J Anaesth 1992;39:458-65.
8. Lenox WC, Mitzner W, Hirshman CA. Mechanism of thiopental-induced constriction of guinea pig trachea. Anesthesiology 1990;72:921-5 .
9. Curry CC, Lenox WC, Spannhake EW, Hirshman CA. Contractile responses of guinea pig trachea to oxybarbiturates and thiobarbiturates. Anesthesiology 1991;75: 679-83.
10. Eames WO, Rooke GA, Wu RS-C, Bishop MJ. Comparison of the effects of etomidate, propofol and thiopental on respiratory resistance after tracheal
1. intubation. Anesthesiology 1996;84:1307-11.
11. Groeben H, Schlicht M, Stieglitz S, Pavlakovic G, Peters J. Both local anesthetic-, and salbutamol pretreatment affect reflex broncho-constriction in volunteers with asthma undergoing awake fiber optic intubation. Anesthesiology 2002;97:1445-50.
12. leff AR. Identifying patients at risk from the use of beta-adrenergic agonist (editorial) Am J Respir Crit Care Med 1996; 154: 1593.
13. Suissa S, Hemmelgam B, Blais L, Ernst P. Bronchodilators and acute cardiac death. Am J Respir Crit Care Med 1996;154:1589-602.
14. Lipworth BJ, Clark RA, Fraser CG, McDevitt DG. The biochemical effects of high-dose inhaled salbutamol in patients with asthma. Eur J Clin Pharmacol 1989;36:357-60.
15. Wong CS, Pavord ID, Williams J, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalemic effects of fenoterol, salbutamol, and terbutaline in asthma. Lancet 1990;336:1396-9.

16. Barnes PJ. Mechanisms of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996;154:821-7.
17. Gal TJ. Bronchial hyper responsiveness and anesthesia. Physiologic and therapeutic perspectives. Anesth Analg 1994;78:559-73.
18. Sauder RA, Lenox WC, Tobias JD, Hirshman CA. Methylprednisolone increases sensitivity to beta-adrenergic agonists within 48 hours in basenji-greyhounds. Anesthesiology 1993;79:1278-83.
19. Greos LS, Vichyanond P, Bloedow DC, Irvin CG, Larsen GL, Szefler SJ, Hill MR. Methylprednisolone achieves greater concentrations in the lung than prednisolone, a pharmacokinetic analysis. Am Rev Respir Dis 1991;144:586-92.
20. Pien LC, Grammar LC, Patterson R. Minimal complications in a surgical population wirh severe asthma receiving prophylactic corticosteroids. J Allergy Clin Immunol 1988;82:696-700.