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Original Article

Perioperative corticosteroids for intermittent and mild persistent asthma

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ABSTRACT

Objectives: Asthmatics are considered to be at high risk for pulmonary complications during general anesthesia with tracheal intubation. The purpose of the present study was to determine the usefulness of perioperative corticosteroids for mild asthmatics in preventing perioperative exacerbation of asthma.

Methods: Airway hyperresponsiveness to inhaled methacholine was determined in patients with intermittent (n = 27) and mild persistent (n = 48) asthma before general anesthesia who underwent surgery between January 1990 and January 1999. All patients 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. Airway hyperresponsiveness to inhaled methacholine was determined in six other asthmatics before and after a similar regimen of perioperative corticosteroids treatment.

Results: Only three cases (4.0%) developed mild asthma during the perioperative period. No evidence of adverse effects of corticosteroids was noted in any case. The use of the same therapeutic regimen in another six asthmatics significantly suppressed airway hyperresponsiveness to inhaled methacholine.

Conclusions: Our results suggest that perioperative corticosteroids are effective in preventing perioperative bronchospasm in stable asthmatics during surgery under general anesthesia by suppressing airway hyperresponsiveness.

Key words: airway hyperresponsiveness, bronchial asthma, general anesthesia, perioperative bronchospasm.

INTRODUCTION

Patients with asthma show airway hyperresponsiveness (AHR) to various stimuli, airway obstruction and mucus hypersecretion and, thus, are thought to be at high risk for pulmonary complications during general anesthesia with tracheal intubation.[1] The recent increase in the prevalence of asthma[2,3] suggests that the number of asthmatics undergoing surgery will also increase in the future. Pulmonary function is one of the most important determinants of prognosis in asthmatics undergoing surgery, especially chest surgery.[4,5] Even when the preoperative lung function is normal, severe lung dysfunction could develop in asthmatics due to various stimuli and medications administered throughout perioperative procedures. Several investigators have reported that the incidence of pulmonary complications is higher in patients with asthma than in those without asthma.[6,7] Surgery should be performed in patients with active asthma following thorough treatment including corticosteroids (CSs), with the exception of emergency cases. While the importance of perioperative CSs for mild asymptomatic asthmatics is controversial,[8–10] the perioperative treatment protocol for mild and stable asthmatics with

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previous attacks or for patients with AHR but without any history of asthma attacks is yet to be established.

Bronchial asthma is a chronic airway inflammatory disease, characterized by cellular infiltration into the airways, including mast cells, B cells, T cells and eosinophils. Airway hyperresponsiveness in asthma is linked to chronic allergic inflammation of the airway.[11,12] Corticosteroids are one of the most effective therapeutic agents for asthma. Although the precise mode of action is still unknown, it is likely that CSs suppress allergic inflammation of the airway and result in the suppression of AHR.[13,14] We hypothesized that perioperative CSs could suppress AHR in asthmatics and prevent operation-induced bronchospasm. Thus, we treated mild asymptomatic asthmatics who required general anesthesia with perioperative CSs. The present study demonstrates the outcome of perioperative CSs for stable asthmatics and the effects of CSs on AHR.

METHODS

Patients

Between January 1990 and January 1999, 75 adult asthmatics were referred by the surgical services to the out-patient clinic of the Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan, before surgery requiring general anesthesia and tracheal intubation. Bronchial asthma was diagnosed and its severity was defined based on the *Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma*.[15] Most patients were new referrals previously treated by general practitioners, while a few were treated by the out-patient clinic of the Second Department of Internal Medicine, Nagasaki University School of Medicine. Atopy was defined when one or more skin prick tests and/or serum allergen-specific IgE (RAST) to 10 common aeroallergens were positive. This study was approved by the Ethics Review Committee of Nagasaki University and written informed consent was obtained from each subject.

Pulmonary function and methacholine inhalation tests

Spirometry and methacholine (MCh) inhalation test were performed on the same day within 2 weeks prior to the operation. All medications were stopped 24 h before the tests and the absence of wheeze was confirmed clinically by chest auscultation. Spirometry was performed with the patient seated, using an electronic spirometer (DISCOM-21FX; Chest, Tokyo, Japan). The MCh inhalation test was performed as reported previously.[16] In brief, MCh aerosol was administered from a hand-held DeVilbiss nebulizer (no. 565ON; DeVilbiss, Somerset, PA, USA) during tidal breathing for 2 min. The operating airflow rate was 5 L/min. Isotonic saline was inhaled first as a control. This was followed by doubling concentrations of MCh from 0.049 to 25 mg/mL. The forced expiratory volume in one second ($FEV_{1.0}$) was measured after each inhalation with a spirometer (DISCOM-21FX; Chest MI, Tokyo, Japan). The fall in $FEV_{1.0}$% was calculated relative to the post-saline $FEV_{1.0}$. The test was continued until $FEV_{1.0}$ had fallen $> 20\%$ or until the maximal concentration of MCh had been administered. Airway hyperresponsiveness was expressed as the cumulative dose of MCh that would provoke a fall in $FEV_{1.0}$ of 20% (PD_{20}). At the end of the test, any fall in $FEV_{1.0}$ was reversed with inhalation of salbutamol.

Protocol

Subjects were treated as follows: oral prednisolone 10–20 mg/day for 1–2 days pre-operatively, methylprednisolone 80–125 mg 2 h before the operation and 80 mg methylprednisolone just after the operation. Enrolment in the present study allowed the subjects to remain on the same medications for asthma. Retrospectively, the incidence of bronchospasm during the perioperative period to 2 weeks after the operation was evaluated from medical records and questionnaires. The incidence of adverse effects of CSs, including signs of wound infection, delay or difficulty in wound healing or wound dehiscence were also evaluated.

During the study period, three asthmatics who were not treated with perioperative CSs developed bronchospasm and the clinical backgrounds of these patients were analyzed from the medical records.

Effects of short-term CSs on AHR

Airway hyperresponsiveness to inhaled methacholine was determined in a different group of six adult asthmatics, who were not to undergo operation, before and after a similar CSs treatment regimen used in the operation group as described above.

Data analysis

Data are expressed as the mean ± SD. The PD_{20} was compared before and after GCs treatment, using the Wilcoxon rank sum test after conversion into logarithmic values because of the high variance.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. All were defined as having intermittent or mild persistent asthma. In most patients, medication consisted of inhaled β_2-adrenergic receptor agonists on demand only, while a small proportion of patients used only beclomethasone dipropionate inhaler (BDI). Because most patients had been treated previously by general practitioners and were seen perioperatively only in our out-patients clinic, the medications prescribed for the subjects seem to be suboptimal. The most frequent surgical area in the present study was the abdomen, followed by the chest. Pulmonary function was normal in all subjects (mean vital capacity 101 ± 16% predicted; mean $FEV_{1.0}$ 88 ± 15% predicted) and MCh inhalation tests demonstrated the presence of AHR in all subjects (mean PD_{20} 1.34 ± 1.44 mg/mL).

Table 1 Patient characteristics

Sex (M/F)	50/25
Age (years)	
Mean	51.5 ± 18.4
Range	16–77
Type of asthma	
Atopic	29
Non-atopic	36
Unknown	10
Severity of asthma	
Intermittent	27
Mild persistent	48
Moderate persistent	0
Severe persistent	0
Therapy	
None	24
Inhaled β_2-adrenergic receptor agonist	44
BDI	7
Oral PSL	0
Operation time (h)	
Mean	4.3 ± 1.9
Range	1.8–8.4
Chest	20
Abdomen	27
Head and neck	13
Limbs	15

Where appropriate, data are the mean ± SD of 75 subjects.
BDI, beclomethasone dipropionate inhalation; PSL, predonisolone.

Outcome of pre-operative CSs treatment

Only three cases (4.0%) developed mild asthma post-operatively and all patients were successfully treated with salbutamol sulfate inhalation. No evidence of adverse effects of CSs was found in any case.

Three asthmatics without pre-operative CSs treatment

Three patients with mild asthma underwent surgery without pre-operative consultation for their asthma by a pulmonary physician. Surgery was performed in these patients without CSs treatment. Table 2 demonstrates the background and episodes of asthma in these three cases. Cases 1 and 2 were categorized as non-atopic, mild persistent asthma and well controlled 1 week prior to the operation by inhaled β_2-adrenergic receptor agonist on demand only. Case 3 was atopic without any history of asthma. She was not on any medication and had normal pulmonary function tests. Anesthesia was induced in all cases by fentanyl and cases 1 and 2 were maintained by nitrous oxide and isoflurane (nitrous oxide–oxygen–isoflurane (GOI)). Case 1 developed a severe asthma attack 18 h after the operation. Case 2 developed bronchospasm at the time of extubation and subsequently became poorly controlled. The operation for case 3 was cancelled because of severe bronchospasm at intubation. Subsequently, case 3 presented with typical asthma attacks. These episodes were treated with CSs and all cases were well controlled by BDI. At the second skin grafting for case 2 and at reoperation for case 3, these patients received perioperative CSs and neither developed pulmonary complications. Clinically, allergy to drugs or latex was not identified in these three patients.

Effects of short-term CSs on AHR

Airway hyperresponsiveness was determined before and after a similar CSs treatment in another group of six adult asthmatics (male : female ratio 4 : 2; mean age 46.3 ± 9.8 years; atopic : non-atopic ratio 3 : 3). The same dose of CSs for perioperative treatment significantly ($P < 0.05$) reduced AHR to inhaled MCh (1.48 ± 1.36 *vs* 8.42 ± 9.65 mg/mL before and after CSs, respectively; Fig. 1).

Table 2 Three cases who were not treated with steroids pre-operatively

	Case 1	Case 2	Case 3
Age (years)/Sex	65/M	68/M	32/F
Asthma duration (years)	7	Unknown	0
Type of asthma	Non-atopic	Non-atopic	Atopic
Severity of asthma	Mild persistent	Mild persistent	–
Therapy before operation	T, β	T	None
VC (% predicted)	102.2	ND	90.0
$FEV_{1.0}$/FVC (%)	88.3	ND	92.3
PD_{20} (mg/dL)	0.15	ND	2.06
Surgery diagnosis	Esophageal cancer	Systemic burn	PDA
Procedures	Esophagectomy	Skin grafting	–*
Duration (h : min)	04 : 05	04 : 45	–*
Induction	Fentanyl	Fentanyl	Fentanyl
Maintenance	GOI	GOI	–*
Episodes	Severe attack at 18 h postop.	Bronchospasm at extubation	Bronchospasm at intubation

*The operation was cancelled due to intubation-induced bronchospasm.

T, sustained release theophiline; β, inhaled β_2-adrenergic receptor agonist as needed for symptoms; GOI, nitrous oxide and isoflorane; PDA, patent ductus arteriosus; ND; not done; VC, vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity.

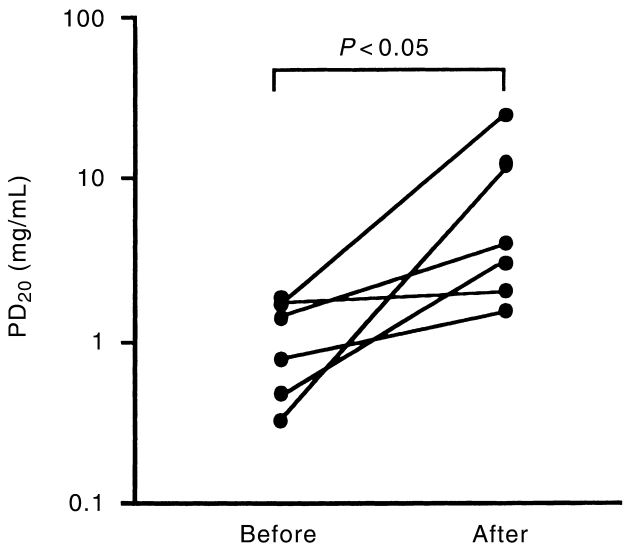

Fig. 1 Airway hyperresponsiveness to inhaled methacholine before and after corticosteroid treatment in six asthmatics.

Discussion

A key finding of the present study is that perioperative CSs are effective in preventing perioperative bronchospasm in steroid-independent mild asthmatics during surgery under general anesthesia. Patients with asthma undergoing surgery requiring general anesthesia are classified into one of the following categories:[17] (i) patients in continuous asymptomatic periods without any medication; (ii) patients with unstable asthma; and (iii) patients in transient asymptomatic periods with anti-asthma medications. It is necessary for asthmatics classified as category (ii) or (iii) to be adequately treated before operation, including the use of CSs, excluding, of course, emergency cases. At this stage, however, it is uncertain whether pre-operative anti-asthma treatment is necessary for patients in category (i). The *Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma*[15] recommends CSs treatment for patients showing perioperative pulmonary dysfunction and CSs dependence. In the present study, we treated asthmatics undergoing surgery with CSs even for patients in the intermittent or mild persistent categories who had normal pulmonary function tests and showed no evidence of CSs dependence. Case 3 in the present study, who developed bronchospasm during intubation and was not treated with CSs pre-operatively, had no history of asthma, but had AHR. In this regard, we have recently reported that AHR persists in adult subjects outgrowing childhood asthma,[16] suggesting that it is better to suppress AHR by CSs in asymptomatic asthma to prevent pulmonary complications during perioperative periods.

Although a double-blind study design is preferable in order to prove the usefulness of perioperative CSs treatment for the prevention of asthma attacks, it was ethically impossible to do so in the present study. Instead, we included in the present study three cases who developed

asthma without perioperative CSs treatment. All anesthetic reagents known to induce histamine release, bronchoconstriction or cholinergic nerve stimulation are contraindicated for asthmatics (e.g. thiopental and tubocurarine).[7,18] The three cases who did not receive perioperative CSs treatment were maintained by fentanyl, a narcotic agent, and developed asthma attacks. Because fentanyl was used in other asthmatics during the same study period in our hospital and is generally preferred for asthmatics, it is unlikely that fentanyl induced the asthma attacks in these three subjects. Anesthesia was maintained in cases 1 and 2 by isoflurane. Isoflurane induces broncodilatation similar to halothane and is often used for asthmatics.[19] Although rare, isoflurane also induces bronchoconstriction in some patients.[20] However, it is unlikely that isoflurane caused bronchoconstriction in these two cases because they developed asthma attacks after surgery. Various stimuli during operation, including intubation and extubation, may have caused bronchospasm in these three subjects with AHR, irrespective of the anesthetic reagent used.

The *Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma* recommendations for the treatment of mild persistent asthma are either inhaled CSs or cromolyn,[15] whereas only seven of 48 patients used inhaled CSs in the present study, suggesting suboptimal treatment. Because long-term use of inhaled CSs suppresses AHR,[21] optimal treatment with inhaled CSs in the weeks prior to surgery may have been adequate to prevent perioperative complications without having to administer systemic CSs. To date, it is uncertain whether short-term oral and/or intravenous CSs can inhibit AHR.[22,23] Thus, AHR was determined in a different set of asthmatics before and after CSs similar to the preoperative CSs treatment. Our results indicate that short-term oral and intravenous CSs significantly inhibit AHR. Compared with inhaled CSs, our protocol with oral and intravenous CSs requires a shorter treatment period and has a clear advantage regarding compliance with therapy. The doses of CSs used in the present study were based on the regular dose for acute asthma. Thus, a comparative study using different doses of CSs will be planed as our next study to determine the adequate CSs doses for use in intermittent and mild persistent asthmatics during surgery.

Although the present study was not performed in a double-blinded fashion, as mentioned above, neither severe attacks nor CSs-induced adverse effects[24] occurred. We conclude that pre-operative CSs treatment for asthmatics, even for patients in the intermittent or mild persistent categories, is advisable to prevent operation-induced asthma attacks by, at least partly, inhibiting AHR.

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