Original Article

Lung protective effects of budesonide nebulization during perioperative period of thoracolumbar fusion

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Objective: To determine the pulmonary protective effect of budesonide nebulization in patients undergoing spinal fusion for thoracolumbar degenerative disorders.

Methods: Forty patients who underwent spinal fusion at our hospital from January 2013 to December 2013 for the treatment of thoracolumbar degenerative disorders were randomly allocated into a budesonide intervention group (budesonide group) and a control group. The control group received routine supportive therapy including rehydration, analgesia, and neurotrophic drug treatment; in addition to these, the budesonide group was administered with budesonide nebulization (1-mg budesonide/2-mL saline, twice daily) from 1 day preoperatively through 3 days postoperatively. Respiratory symptoms, arterial blood gas, and pulmonary complication before and after the operations were observed and compared between the two groups.

Results: The patients ranged in age from 46 to 81 years old (mean, 62.4±9.4 years), and comprised 20 men and 20 women. There were no significant differences in postoperative body temperature, heart rate, and respiratory rate between the groups (P>0.05). The change in arterial partial pressure of oxygen (PaO_2) from baseline was significantly lower in the budesonide group than in the control group (at 2.4±12.4 *vs.* 16.0±11.3 mmHg) (P=0.002), so was the findings for oxygen saturation (SpO_2) (0.2%±2.3% *vs.* 2.6%±3.3%), respectively (P=0.047). The incidence of postoperative pulmonary symptoms and complications, such as coughing, shortness of breath, and dyspnea, was 0% in the budesonide group and 15% in the control group; overall, the budesonide group performed better than control group in all pulmonary parameters. None of the patients in the budesonide group experienced severe events associated with glucocorticoid therapy.

Conclusions: Perioperative budesonide nebulization may reduce the postoperative pulmonary complications in middle-aged and elderly patients undergoing thoracolumbar fusion to treat thoracolumbar degeneration, with favorable efficacy and safety.

Keywords: Nebulization; budesonide; thoracolumbar degenerative disease; perioperative period; lung protection

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Introduction

Indications for orthopaedic surgeries are expanding along with the advance of medical sciences and techniques. As China evolves into an aging society, a significant percentage of middle-aged and elderly patients undergo surgery for degenerative thoracolumbar disorders each year. Compared with younger age groups, elder patients usually present with multiple pulmonary and cardiovascular co-morbidities, weakened airway defense, and in males, a long history of cigarette smoking (1,2). Several perioperative factors have been shown to affect the airway and reduce postoperative pulmonary function, resulting in a variety of respiratory complications such as pulmonary atelectasis, pneumonia, bronchospasm, respiratory failure, and acute respiratory distress syndrome (3-6). Pulmonary conditions are among the most common complications following thoracolumbar

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fusion (5,7), with the perioperative incidence being 5.5% and 7%, respectively, in patients with thoracic and lumbar spinal stenosis. In addition, the incidence of respiratory complication is closely related to the 2-year mortality (relative risk: 10.76) (6). Proactive prevention against pulmonary complications is therefore essential to improve the surgical outcomes and facilitate postoperative recovery in the elderly.

Budesonide is a glucocorticoid typically administered through nebulization. In addition to its powerful anti-inflammatory actions, budesonide may also reduce airway edema, inhibit airway remodeling, and is widely used in treating chronic obstructive pulmonary disease, asthma and many other pulmonary disorders (8-10). During the recent years, perioperative use of budesonide in selected patients for cardiac surgery, thoracic surgery and other procedures has yielded satisfactory pulmonary protective effects (11-15). Pulmonary protection associated with perioperative budesonide nebulization has not been reported in middle-aged or elderly patients undergoing spinal fusion for treatment of thoracolumbar degenerative diseases. We set out to investigate whether budesonide inhaled perioperatively protects against occurrence of pulmonary complications in this subset of patients.

Patients and methods

Patient selection

Between January 2013 and December 2013, forty middle-aged or elderly subjects were randomly selected from all patients undergoing thoracolumbar fusion at the Orthopaedics Department of Peking Union Medical College Hospital. The inclusion criteria were: (I) a confirmed diagnosis of degenerative thoracolumbar disease based on clinical findings and imaging studies; (II) age above 45 years old; (III) risk factors for perioperative pulmonary complications (such as advanced aged >65; BMI ≥28.0; preoperative bedridden time ≥3 days; smoking index ≥400; previous cardiac events; diabetes; cerebrovascular disease; COPD; hypertension; anemia; ASA classification >2; FEV1 ratio ≤65%; operation time ≥3 hours); (IV) with surgical indications for posterior spinal fusion; (V) use of general anesthesia; and (VI) no difficulty in verbal and written communication in Chinese. The exclusion criteria were: (I) use of systemic glucocorticoids within the four weeks prior to surgery; (II) any contraindication for the medication with budesonide, such as drug-related hypersensitivity; (III) necessity of perioperative mechanical ventilation; and (IV) severe co-morbidities of the heart, lung, liver or other vital organs. Those with concomitant trauma of the chest, abdomen or the head, or signs of adrenocortical dysfunction, pregnant or lactating women, and patients who refused to participate in the study were also excluded.

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. All enrolled patients gave informed written consent before entering the study.

Study design and patient treatments

The 40 patients were divided into the control and budesonide groups comprising 20 individuals each using a random number table. All patients underwent general anesthesia with endotracheal intubation before total laminectomy and spinal fusion. All surgeries were performed by the same orthopaedic surgical team. All patients received routine supportive care such as rehydration, analgesia, and neurotrophic drug treatment postoperatively. Antibiotics were discontinued 24 h postoperatively. Non-steroidal anti-inflammatory drugs were administered perioperatively to relieve pain.

In addition, the budesonide group was given 1 mg Pulmicort Respules (budesonide inhalation suspension, AstraZeneca Plc., Sweden) dissolved in 2 mL of normal saline delivered by nebulization (PARI LC Disposable Nebulizer, PARI GmbH., Germany) from days 1 through 3 postoperatively. Instructions to these patients to ensure proper use of budesonide nebulization were given and enhanced before and after the surgical operations. The nebulization lasted 20 min for each session and was performed twice daily (at 9 am and 3 pm).

The investigators of this study were blinded to group assignment; thus, all perioperative data were evaluated in a single-blinded manner.

Data collection

Pulmonary function parameters were measured using spirometry (Master Screen IOS, JAEGER, Germany) 1 day before nebulization: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. Arterial blood gas analysis was performed when the patients were breathing room air at 1 day before nebulization and at 3 days postoperatively after discontinuing nebulization (4 pm) to estimate pulmonary ventilation and air exchange functions.

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Table 1 Patient demographics and pulmonary function at baseline in control and budesonide groups ($\bar{x}\pm s$)

Characteristic	Budesonide group	Control group	P value
Sample size (n)	20	20	
General information			
Gender (male/female)	11/9	9/11	0.527
Age (years)	59.9±10.3	60.1±13.5	0.949
Height (cm)	166.5±7.2	162.3±8.3	0.087
Body weight (kg)	71.7±9.1	70.3±12.4	0.680
BMI	25.7±3.1	26.8±4.8	0.399
Smoking history-persistent smokers (n)	5	6	0.723
Indexes of preoperative lung function examination			
FEV_1 (%)	100.1±13.9	98.0±13.2	0.651
FVC (L)	3.4±0.8	3.1±0.8	0.253
FEV_1/FVC (%)	77.4±6.3	74.4±14.4	0.782

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 2 Intraoperative clinical data in the control and budesonide groups ($\bar{x}\pm s$)

Group	Difficult airway, N [%]	Endotracheal intubation time (min)	Blood loss (mL)
Budesonide group	3 [15]	248.3±85.5	740.4±472.7
Control group	3 [15]	231.1±56.5	550.0±266.6
P value		0.744	0.221

Intraoperatively, presence of a difficult airway (16), endotracheal intubation time, and blood loss were recorded.

Clinical data were observed and recorded daily as follows: (I) general vital signs including body temperature, heart rate, and respiratory rate; (II) pulmonary complications including atelectasis, pneumonia, respiratory failure, bronchospasm, pulmonary embolism, and pulmonary edema, which were diagnosed based on clinical symptoms (coughing, sputum, wheezing, dyspnea), physical checkup, imaging and pathological studies; and (III) nebulization-related adverse reactions: symptoms and clinical signs attributable to glucocorticoids or drug administration (nausea or vomiting) during observation (from the beginning of nebulization to hospital discharge), apart from allergic reactions secondary to other drugs. Adverse reactions were classified into three categories according to severity: mild, with tolerable symptoms or vital signs; moderate, modest interference with normal activities; and severe, noted by severe adverse reactions and inability for normal activities (17).

Statistical analysis

All numerical data were expressed as mean ± standard deviation (SD). Normally distributed data were compared using the independent sample t test, and non-normally distributed data using the rank sum test. Enumeration data were expressed as sample size and percentage, and analyzed using the Chi-square test or Fisher's exact test. A P value less than 0.05 was considered statistically significant. All data were processed using PASW Statistics for Windows (Version 18.0, SPSS Inc., Chicago, USA).

Results

Patient demographics at baseline

In total, there were 40 patients included in this study, comprising 20 men (50%) and 20 women (50%) aged 46-81 years (mean: 62.4±9.4 years). Before the operations (baseline), there were no statistically significant differences between the two groups with respect to age, height, body weight, BMI, and gender ratio (all P>0.05), as shown in *Table 1*. Five patients in the budesonide group and six in the control group had a smoking history (P=0.723). The three pulmonary function indices, FEV_1, FVC, and FEV_1/FVC, were not significantly different between the two groups (all P>0.05), as shown in *Table 1*.

Intraoperative data

Three patients (15%) each in the budesonide and control groups had a combined difficult airway due to previous cervical vertebral surgery. The both groups did not differ statistically in intraoperative endotracheal intubation time or blood loss, as shown in *Table 2*.

Arterial blood gas

There were no significant differences in the preoperative

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Table 3 Pre- and postoperative arterial blood gas analysis in the budesonide and control groups ($\bar{x}\pm s$)

Arterial blood gas analysis	Budesonide group	Control group	P value
PaO_2 (mmHg)			
Preoperative	79.2±10.9	82.7±10.6	0.304
Postoperative	76.6±9.4	72.0±11.7	
Difference (preoperative-postoperative)	2.4±12.4	16.0±11.3	0.002*
$PaCO_2$ (mmHg)			
Preoperative	39.2±3.8	40.4±3.6	0.314
Postoperative	35.5±4.5	39.2±3.2	
Difference (preoperative-postoperative)	3.8±4.2	1.1±3.7	0.063
SpO_2 (%)			
Preoperative	95.6±1.8	96.2±1.8	0.292
Postoperative	95.3±2.1	94.3±3.3	
Difference (preoperative-postoperative)	0.2±2.3	2.6±3.3	0.047*

*Compared to the control group P<0.05.

arterial blood gas analyses (PaO_2, $PaCO_2$, SpO_2) between the two groups (P>0.05); however, the reduction in levels of postoperative PaO_2 and SpO_2 from pre-operation was significantly less in the budesonide group than the findings in the control group (P<0.05), as summarized in *Table 3*.

Postoperative vital signs

General vital signs including body temperature, heart rate, and respiratory rate during preoperative days 1 through 3 days did not show significant differences between the groups (P>0.05), as shown in *Table 4*, suggesting that budesonide nebulization perioperatively did not significantly influence the general postoperative vital signs.

Pulmonary symptoms and complications

No patients in the budesonide group experienced respiratory symptoms such as coughing, expectoration, or wheezing. Three patients (15%) in the control group experienced respiratory symptoms during the study period: two patients (10%) reported coughing and expectoration on the postoperative day 2, and one (5%) reported wheezing and dyspnea on postoperative day 3. All symptoms resolved after symptomatic and supportive treatment, and there were no significant findings in imaging and pathological studies. The budesonide group did not experience any pulmonary complications, compared with one patient in the control group diagnosed with pneumonia based on imaging study and clinical signs including fever, coughing, and expectoration. The patient was given medical treatment and recovered uneventfully.

Table 4 Vital sign compared between the budesonide and control groups ($\bar{x}\pm s$)

Time	Group		P value
	Budesonide group	Control group	
Pre			
T (℃)	36.5±0.3	36.6±0.3	0.584
HR (bpm)	78.4±11.5	80.4±13.3	0.597
RR (breaths/min)	18.5±1.3	19.0±1.4	0.367
Day 1			
T (℃)	37.0±0.45	37.0±0.38	0.576
HR (bpm)	80.0±6.0	77.2±6.5	0.149
RR (breaths/min)	18.8±1.0	18.7±0.9	0.681
Day 2			
T (℃)	36.9±0.4	37.0±0.5	0.444
HR (bpm)	79.5±5.8	78.6±4.4	0.618
RR (breaths/min)	18.8±1.0	18.8±0.6	0.892
Day 3			
T (℃)	36.8±0.39	36.8±0.39	0.455
HR (bpm)	78.7±5.5	78.0±4.5	0.407
RR (breaths/min)	18.8±0.7	18.7±0.7	0.458

Pre, before operation; Day 1, 1st day postoperatively; Day 2, 2nd day postoperatively; Day 3, 3rd day postoperatively; T, temperature; HR, heart rate; RR, respiratory rate.

None patients of the budesonide group experienced events associated with glucocorticoid administration such as allergic reactions, oropharyngeal disease, and systemic reactions. One patient (5%) had a local discomfort related to nebulization, manifesting as nausea during nebulization on the first postoperative day. The patient's vital signs were stable; the adverse event was deemed attributed to the nebulization procedure, and classified as a mild adverse reaction according to the described classification standards. He recovered with bed-rest and did not require additional treatment.

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Discussion

This randomized controlled study indicated that perioperative budesonide nebulization reduced fluctuations in PaO_2 and SpO_2, and was associated with lower incidence of pulmonary symptoms such as coughing, wheezing, and dyspnea, and pulmonary complications in middle-aged and elderly patients after thoracolumbar fusion. None patients of the budesonide group experienced complications associated with glucocorticoids such as allergic reactions, oropharyngeal disease, and systemic reactions. Moreover, nebulization as administered in this study (1-mg budesonide in 2-mL saline given twice daily from 1 day preoperatively to 3 days postoperatively) was safe and effective for perioperative clinical care.

During thoracolumbar fusion, perioperative pulmonary complications associated with patient age warrant consideration (4,18,19). In degenerative thoracolumbar spinal diseases, a variety of factors can affect occurrence of perioperative pulmonary complications. Preoperative factors include advanced age, cardiopulmonary disease, and a long history of smoking, impaired airway defensive capacity; intraoperative factors such as placement in a prone position, long surgical duration, large surgical incision, endotracheal intubation, anesthetic drugs, and mechanical ventilation, can in many ways stimulate the airway by destroying the respiratory barrier, damaging the tracheal mucosa, and reducing the lung compliance. Postoperative factors such as pain and immobilization limit coughing, prevents discharge of airway secretions. These numerous factors can result in a series of perioperative pulmonary complications such as atelectasis, pneumonia, and bronchospasm. In the 40 middle-aged and elderly patients included in this study, the incidence of pulmonary complications was 2.5% and 5% in the control group. In a clinical study with large sample sizs, He *et al*. (7) reported a 5.5% perioperative incidence rate of pulmonary complication in thoracic spinal stenosis patients; Lee *et al*. reported a 7% incidence after lumbar surgery and 13% after spinal surgery (6). The pulmonary complication rate in this study was slightly lower than that reported previously, most probably as a result of rigorous criteria for patient inclusion. In order to control for potential confounders and more objectively evaluate the pulmonary protective effect of budesonide nebulization, patients requiring perioperative mechanical ventilation, concurrent severe or uncontrolled systemic disease such as vital organ failure, concurrent thoracic, abdominal, and head trauma, and those at high risk of severe pulmonary complications were excluded.

Pulmonary protection refers to proactive prevention and treatment of imminent pulmonary injury of various etiologies (20). An appropriate protective strategy during the perioperative period of thoracolumbar fusion can effectively maintain pulmonary function and prevent related complications. This ensures that the patient safely survives the perioperative period and strongly supports the effectiveness of the operation to help patients recover faster.

Budesonide as an inhaled glucocorticoid may effectively inhibit a variety of inflammatory cells, reduces the generation of inflammatory mediators, and exhibits significant anti-inflammatory effect; in the airway, it also induces vessel contraction, inhibits mucosal edema, reduces cell exudation, mitigates edema, and prevents airway remodeling (21-24). Compared to systemic glucocorticoids, such as dexamethasone and hydrocortisone, budesonide nebulization offers the following unique benefits: (I) high concentration primarily in the lungs; (II) high hepatic clearance; and (III) high glucocorticoid receptor affinity. During nebulization, the nebulizer unit breaks the liquid into micro-particles, which are directly inhaled into the lower respiratory tract and rapidly absorbed by the pulmonary mucosa, thus increasing the local drug concentration. It also hydrates the airways, which dilutes airway secretions and facilitates their discharge.

For patients undergoing thoracolumbar fusion, the pharmacologic and pharmacokinetics characteristics of budesonide, combined with local administration using nebulization effectively prevents airway inflammation, alleviates edema, inhibits airway remodeling, and promotes expectoration, which maintains pulmonary function and reduces adverse events associated with glucocorticoid accumulation, such as hypothalamic-pituitary-adrenal axis suppression, bone demineralization, and growth inhibition (25,26). Budesonide nebulization could function as a pulmonary protectant during the perioperative period of thoracolumbar fusion.

This randomized controlled study is the first attempt to evaluate the pulmonary protective effect of budesonide nebulization during perioperative thoracolumbar fusion in middle-aged and elderly patients. Preoperative factors such as age, general health, pulmonary function, and smoking history, which are associated with perioperative pulmonary complications, were consistent between the budesonide and control patients. Reportedly, the presence of a difficult airway affects respiratory function during the perioperative period (16); endotracheal intubation time and the surgical

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trauma severity also influence the pulmonary complication rate after spinal surgery (6). In this study, the intraoperative blood loss was an indicator for severity of surgical trauma. There were no statistically significant differences intraoperatively between the two groups. Postoperatively, the budesonide group showed remarkably less reduction from baseline in PaO_2 and SpO_2 as compared with the control group ($P<0.05$). In addition, incidence of respiratory symptoms such as coughing, asthma, and dyspnea was 15% in the control group, and one (5%) postoperative pneumonia case was observed; the incidences of pulmonary symptoms and complications were higher in the control group than in the budesonide group. These findings indicate that budesonide nebulization perioperatively has a pulmonary protective effect in middle-aged and elderly patients with degenerative thoracolumbar disease, and specifically, nebulization administered as presently described (1-mg budesonide/2-mL saline, twice daily, from 1 day preoperatively to 3 days postoperatively) is clinically effective.

Recently, budesonide has been used more widely perioperatively in several surgical fields including cardiac, thoracic, and abdominal surgeries, and the treatment has achieved good effects (12,14,27-29). Fang *et al*. (12) evaluated the effect of budesonide nebulization on pulmonary function in a study of 22 elderly patients undergoing abdominal surgery and found that pre- and intraoperative budesonide inhalation improved pulmonary ventilation with no impact on respiratory mechanics. In a randomized controlled study, Ju *et al*. (14) evaluated the effect of preoperative budesonide nebulization on inflammation in thoracotomy patients receiving single-lung ventilation and revealed that preoperative budesonide nebulization reduced the peak airway pressure and plateau pressure, increased pulmonary compliance, inhibited inflammation, and ultimately improved pulmonary function. A study conducted by Sawada *et al*. (28) also confirmed the effectiveness of preoperative budesonide nebulization in thoracic surgery patients. Collectively, the results of these prior studies and the current study show that perioperative budesonide nebulization can provide effective pulmonary protection in numerous procedures.

In this study, inhaled corticosteroids in the budesonide group were given in a short duration and low dose. General vital signs such as body temperature, heart rate, and respiratory rate during this period were similar between the groups, and none of the patients experienced allergic reactions, oropharyngeal disease secondary to glucocorticoid nebulization, or systemic adverse reactions; only one patient reported transient nausea following nebulization, which resolved after a short period of rest. These results indicate that in the targeted patient population, short-course perioperative budesonide nebulization as administered in the present study protocol was safe. Presumably, the local administration of budesonide restricted its effect on the lung; this, combined with a higher hepatic clearance, causes fewer systemic adverse reactions compared to intravenous glucocorticoid administration. Previous reports indicate that systemic reactions and oropharyngeal complications caused by budesonide depended on the dosage and treatment duration and occurred solely in patients receiving long-term and large-dosages. Otherwise, adverse reactions were mostly mild, and the complication rate of short-course budesonide treatment was low (8,30,31). Both the present study and previous studies confirm that short-course low-dose budesonide treatment during perioperative thoracolumbar fusion is clinically safe. Budesonide was well tolerated and had a low rate of allergic reactions; however, there are individual reports of delayed allergic reactions following budesonide nebulization (32,33). Although none of the patients experienced an allergic reaction, this complication should be considered in future clinical application of budesonide.

There were several potential limitations in this study. The sample size was small, and patients were not stratified according to factors such as age and smoking history. Correlation factors analysis of pulmonary complications was not performed due to the small sample size. In addition, postoperative follow-up with pulmonary function test was not performed due to potential pain and inconvenience to the patient, and other factors. These limitations may introduce bias in evaluating the clinical effectiveness of budesonide nebulization. Therefore our findings need further validation in future large-sample studies.

In conclusion, perioperative budesonide nebulization may reduce the incidence of pulmonary complications and improved clinical symptoms in middle-aged and elderly patients with thoracolumbar degeneration undergoing spinal fusion. Perioperative budesonide inhalation in this patient population is also tolerable.

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