—**Original**—

Preoperative Administration of Methylprednisolone Attenuates Cytokine-induced Respiratory Failure After Esophageal Resection

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Abstract

Proinflammatory cytokines have been implicated in mediating respiratory failure associated with major surgery. We investigated the effect of giving glucocorticoids preoperatively for the prophylaxis of surgical stress and the association of cytokine levels, such as interleukin-6 (IL-6) and interleukin-8 (IL-8), with oxygenation after esophagectomy. We studied 17 patients who underwent subtotal esophagectomy. Seven patients (steroid group) were chosen at random to be given methylprednisolone (10 mg/kg) and 10 patients (control group) to be given saline intravenously before operation. Plasma and bronchoalveolar lavage fluid (BALF) IL-8 levels in the control group were significantly higher than those in the steroid group. In both groups, plasma IL-6 levels were significantly higher than those in BALF, but in contrast, BALF IL-8 levels were significantly higher than plasma levels of IL-8 postoperatively. The PaO_2/FiO_2 ratio was significantly reduced in the control group. The PaO_2/FiO_2 ratio of the control group had significantly lower values than that of the steroid group. There was significant correlation between BALF IL-8 levels and the PaO_2/FiO_2 ratio postoperatively. We conclude that preoperative administration of methylprednisolone may attenuate postoperative reduction of arterial oxygen saturation by suppressing the release of cytokines.

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Key words: glucocorticoid, interleukin-6, interleukin-8, proinflammatory cytokines, surgical stress

Introduction

Major surgery is associated with a transient severe inflammatory response involving the release of proinflammatory cytokines and leads to systemic inflammation, which may be accompanied by cytokine-induced respiratory failure[1]. Esophagectomy for esophageal carcinoma is one of the most invasive surgical procedures and is associated with a generalized systemic inflammatory response characterized by the activation of proinflammatory cytokines and other chemical mediators[2]. This inflammatory response after esophagectomy may lead to the development of postoperative complications[3]. Pulmonary complications in particular can be fatal, and postoperative hypoxemia is a major cause of anastomotic leaks. Furthermore, increased

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proinflammatory cytokine exists in bronchoalveolar lavage fluid (BALF) in respiratory failure[4-6].

It has been reported that glucocorticoids have been effective in suppressing the inflammatory response secondary to sepsis and other stress-related disease states[7-9]. We have previously reported that preoperative methylprednisolone administration attenuates the metabolic response and enables adequate postoperative oxygenation after esophagectomy[10]. However, the relationship between proinflammatory cytokines and postoperative oxygenation in patients undergoing esophagectomy has not yet been elucidated. It is important to examine the effects of surgical stress on the systemic and pulmonary responses of proinflammatory cytokines. We investigated whether glucocorticoids protected against elevation of proinflammatory cytokine levels after esophagectomy and whether the increase in cytokine was associated with changes in postoperative oxygenation.

Patients and Methods

Informed consent to participate in this study involving the use of methylprednisolone and BAL was obtained from all patients before operation. We studied 17 adults with squamous cell carcinoma of the thoracic esophagus without circulatory, respiratory, or associated metabolic diseases. The patients were randomly divided into two groups: 7 subjects were given methylprednisolone sodium succinate 10 mg/kg (diluted with 50 m*l* saline) intravenously (steroid group), and 10 were given normal saline 50 m*l* as a control group, each given before the induction of anesthesia. General anesthesia was induced with fentanyl (5 μg/kg), midazolam (0.2 mg/kg), and vecuronium (0.1 mg/kg), and was maintained using fentanyl, sevoflurane, nitrous oxide, and oxygen. The patients were placed on a ventilator, and the tidal volume and respiratory rate were adjusted to maintain normocapnia ($PaCO_2$: 35 mmHg to 45 mmHg). All patients underwent subtotal esophagectomy via right thoracotomy, followed by reconstruction with a gastric tube in the chest or neck and three-field (thoracic, abdominal, and cervical) lymphnode dissection. The patients were taken to the intensive care unit (ICU) after the operation, and received continuous sedation with fentanyl (1.5 μg/kg/h) and midazolam (1～4 mg/h). In the ICU, all of the patients were routinely ventilated (Servo ventilator 900 C, Siemens Elema, Sweden). The ventilatory mode was the pressure support mode with positive end-expiratory pressure. The patients were extubated from postoperative day (POD) 3, whenever rapid shallow respiration had ceased, the PaO_2 (mmHg)/inspired oxygen fraction (PaO_2/FiO_2) ratio had reached 250, and the cough reflex had returned.

The plasma and BALF levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) were measured after operation and on POD 1 as indicators of response to surgical injury. A bronchofiberscope was wedged in a segmental bronchus of the right middle lobe to perform BAL. Fifty milliliters of warmed saline was instilled and then gently aspirated immediately thereafter. This procedure was repeated three times. The recovered fluid was promptly filtered through sterile gauze. Arterial blood oxygen saturation was measured with standard blood-gas electrodes (ABL 300, Radiometer, Copenhagen, Denmark). The PaO_2/FiO_2 ratio was used as an index of arterial oxygenation. Blood gas analysis was made on admission to the ICU postoperatively, and in the early mornings of postoperative days 1－3.

Blood and BALF samples were collected in chilled tubes that contained 4% EDTA and into plane tubes, respectively. The samples were kept on ice and immediately centrifuged (3,000 rpm for 20 min, at 4℃), and stored at －70℃ until analysis. The IL-6 and IL-8 levels were measured with enzyme-linked immunosorbent assay kits (IL-6: Toray Fujibionics Inc, Tokyo, Japan; IL-8: R & D systems, Minneapolis, MN, USA). The lower limits of detection in these assays were less than 4 pg/ml for IL-6 and 3 pg/m*l* for IL-8.

Repeated measurement analysis of variance and Bonferroni tests were performed to distinguish postoperative oxygenation within group differences over time. The Mann-Whitney test was used to evaluate differences at the same time periods between the two groups, and the blood and BALF samples. Regression analysis was performed to examine the relationship between pairs of variables. All values are reported as mean (SEM), and all p values less than 0.05 were considered significant.

Table 1 Comparability of the groups

	Control group	Steroid group
Age (years)	60 ± 3	65 ± 1
Sex (male/female)	9/1	6/1
Body weight (kg)	53 ± 2	56 ± 5
Anesthesia time (min)	563 ± 28	546 ± 15
Operation time (min)	467 ± 26	440 ± 19
Blood loss (g)	943 ± 141	819 ± 142
Volume of crystalloid infusion (ml/kg/hr)	8.2 ± 0.6	7.2 ± 0.7
Volume of blood or blood products transfusion (g)	1,065 ± 173	1,211 ± 198

All values are mean ± SEM.

Results

There were no significant differences between the two groups in terms of age, sex, and the operative course (**Table 1**). No patients who developed postoperative complications, such as pneumonia or lung atelectasis, were in both groups during the study period. Also, no anastomotic leaks developed in the steroid group. Plasma and BALF IL-8 levels in the control group were significantly higher than those in the steroid group (**Table 2**). In both groups, plasma IL-6 levels were significantly higher than those in BALF after operation, but in contrast, BALF IL-8 levels were significantly higher than plasma levels of IL-8 after operation and on POD 1. The $PaCO_2/FiO_2$ ratio was significantly reduced in the control group postoperatively, and the control group had significantly lower values than the steroid group on POD 2 and 3 (**Table 3**). There were significant correlations between BALF IL-8 levels after operation and the PaO_2/FiO_2 ratio on POD 2 ($r = -0.75$), and POD 3 ($r = -0.72$). There were also significant correlations between BALF IL-8 levels on POD 1 and the PaO_2/FiO_2 ratio on POD 2 ($r = -0.66$), and POD 3 ($r = -0.70$). However, the PaO_2/FiO_2 ratio did not significantly correlate with other parameters.

Discussion

Our results have shown that methylprednisolone successfully suppresses the release of the indicators of response to surgical injury such as IL-6 and IL-8, and played a significant part in the prevention of postoperative decrease in arterial oxygen saturation.

Nuclear factor kappa B (NF-kappa B) activates many immunoregulatory genes in response to proinflammatory stimuli, and is inhibited by an increase in the rate of production of the I-kappa B alpha inhibitory protein, which traps activated NF-kappa B in inactive cytoplasmic complexes. Glucocorticoids inhibit NF-kappa B activity, which results in induction of I-kappa B alpha inhibitory protein[11,12]. This reduction is thought to reduce cytokine secretion appreciably and so block inflammatory activity[11]. Furthermore, glucocorticoids bind to a cytoplasmic glucocorticoid receptor superfamily, which then translocates to the nucleus as a transcription factor[13]. Transcriptional activation of cytokine and cell adhesion genes is critical in the activation of the inflammation systems and is repressed by glucocorticoids[14]. In the present study, proinflammatory cytokines in the steroid group were significantly lower than those in the control group. Because hypersecretion of proinflammatory cytokines is directly related to surgical stress and has a negative effect on the body, this secretion should be suppressed.

In human and animal models of systemic inflammatory response syndrome (SIRS), four cytokines, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8, are released in a sequential manner, and produce an inflammatory cascade. IL-6 and IL-8 are synthesized by monocytes/macrophages, T-lymphocytes, fibroblasts, and endothelial cells after stimulation by TNF-α and IL-1. However, TNF-α and IL-1 were measured over a relatively short perioperative period and the serum levels of both cytokines were not correlated

Table 2 Changes in the IL-6 and IL-8 levels

IL-6 level		After operation	POD 1
Plasma	Control group	513 ± 194*†	486 ± 292†
	Steroid group	115 ± 15*	92 ± 29
BALF	Control group	125 ± 31	328 ± 121
	Steroid group	53 ± 17	193 ± 104
IL-8 level		**After operation**	**POD 1**
Plasma	Control group	102 ± 25†	60 ± 17†
	Steroid group	29 ± 7	19 ± 3
BALF	Control group	362 ± 65**†	1,061 ± 306**†
	Steroid group	111 ± 37*	225 ± 57**

All values are mean ± SEM.
For differences between the groups: †$p < 0.05$.
For differences between the plasma and BALF levels: *$p < 0.05$, **$p < 0.01$.
IL-6; interleukine-6, IL-8; interleukin-8, BALF; bronchoalveolar lavage fluid.

Table 3 Changes in PaO_2/FiO_2 ratio

	After operation	POD 1	POD 2	POD 3
Control group	464 ± 21	422 ± 16	287 ± 16 *†	257 ± 26 *†
Steroid group	455 ± 41	371 ± 36	371 ± 24	367 ± 41

All values are mean ± SEM.
For differences vs after operation: *$p < 0.01$.
For differences between the groups: †$p < 0.05$.

with the clinical course[15]. In contrast, the IL-6 and IL-8, which are released in the second wave of the cytokine cascade, seem to be good indicators of activation of the inflammatory cascade as well as a predictor of subsequent organ dysfunction and death[1,6,16,17]. The development of SIRS was observed in all patients undergoing esophagectomy, whereas no patients undergoing gastrectomy demonstrated SIRS[18]. Furthermore, serum proinflammatory cytokines after esophagectomy were higher than those after gastrectomy[18]. In the present study, IL-6 and IL-8 levels were very high after esophagectomy. The changes in the PaO_2/FiO_2 ratio were, however, correlated only with the BALF levels of IL-8. the plasma levels of IL-6 were significantly higher than the BALF levels, but in contrast, BALF IL-8 levels were significantly higher than plasma levels of IL-8. These data suggest that elevation of the IL-8 levels in BALF could predict a reduction of postoperative oxygenation. Furthermore, IL-8 in BALF may be one of the many variables that affect postoperative oxygenation, along with pulmonary vascular resistance, sympathetic nervous activity, medications, and other acute phase reactants. IL-8 is related to the development of acute respiratory distress syndrome (ARDS) through recruitment of polymorphonuclear cells in the lung, and an increased IL-8 level is related to the prognosis of ARDS[6,17].

Preoperative methylprednisolone enabled adequate postoperative oxygenation in the present study. The low PaO_2/FiO_2 ratio after esophagectomy seems to be related to a series of responses which predispose to ARDS. The etiology may be related to mechanical lung injury as a result of operation. Pulmonary vascular endothelial cell membranes are particularly vulnerable to surgical stress, and this results in extravascular leak of fluid and albumin secondary to pulmonary vascular hyperpermeability. Methylprednisolone can inhibit lipid peroxidation, protect membrane function from the damaging effects of oxygen radicals[19], as well as induce sufficient lysosome-membrane stabilizing actions[20,21]. A previous study has reported that IL-8 plays important roles in the increase in pulmonary vascular permeability[22]. One of the reasons why postoperative oxygenation was maintained in the steroid group may be that methylprednisolone inhibited pulmonary vascular hyperpermeability resulting from the decrease of IL-8 in blood and BALF.

A relationship between the IL-6 response and the extent of surgical trauma has been reported[1,16]. Cruickshank et al. reported that more severe surgical trauma was associated with a greater increase in serum IL-6 and a higher serum IL-6 concentration[1]. Thus, an excessive and prolonged increase in the circulating IL-6 level is associated with both morbidity and mortality[16]. However, IL-6 was not correlated with the PaO_2/FiO_2 ratio in the present study. Therefore, it should be noted that an increase in IL-6 may be more important for systemic inflammatory responses than for local reactions.

We conclude that preoperative administration of methylprednisolone may attenuate postoperative reduction of arterial oxygen saturation by suppressing the release of cytokines.

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