*Original
Article*

Administration of Corticosteroids, Ascorbic Acid, and Thiamine Improves Oxygenation after Thoracoscopic Esophagectomy

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Purpose: The activity of corticosteroids, ascorbic acid, and thiamine against oxidative and inflammatory responses was evaluated in patients undergoing esophagectomy. This study was undertaken to investigate the effect of this combined therapy on lung dysfunction following esophagectomy.

Methods: In this retrospective before–after study, we compared the clinical course of consecutive patients undergoing thoracoscopic esophagectomy treated with the combination of corticosteroids, ascorbic acid, and thiamine between June and December 2018 with a control group treated with corticosteroids alone between January 2016 and May 2018. Outcomes included oxygenation (arterial partial pressure of oxygen (PaO_2)/fractional concentration of inspired oxygen (FiO_2) ratios), duration of mechanical ventilation and intensive care unit (ICU) length of stay.

Results: In all, 17 patients were included in this study (6 in the combination therapy group and 11 patients in the control group). Mean PaO_2/F_iO_2 ratios in the combined therapy group were significantly higher than in the control group at all points during the observation period (p <0.001). In the combined therapy group, the duration of mechanical ventilation and ICU stay were significantly shorter (p <0.001, p = 0.009).

Conclusions: This study suggests that combined therapy including corticosteroids, ascorbic acid, and thiamine may be effective in improving oxygenation after esophagectomy. Additional studies are required to confirm these preliminary findings.

Keywords: esophagectomy, ascorbic acid, corticosteroids, lung injury

Introduction

Esophagectomy is an invasive surgical procedure.[1] Thoracoscopic esophagectomy is commonly performed resulting in a less invasive operation with less impact on the patient. However, the incidence of perioperative morbidity remains as high as 40%.[2,3] Impaired oxygenation, believed to result from surgical stress and one lung ventilation[4] is a well-known complication of esophagectomy, and requires treatment ranging from oxygen

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supplementation to mechanical ventilation.[5] Oxidative stress and inflammation are believed to play crucial roles in the pathogenesis of impaired oxygenation.[5,6] To improve oxygenation, drugs such as elastase inhibitor[7] or corticosteroids[8,9] are given, but their therapeutic effect has not been confirmed.[7,8,10]

Combination therapy with corticosteroids, ascorbic acid, and thiamine has a prominent therapeutic effect on oxidative stress and inflammatory response.[11,12] These favorable effects can provide significant benefits in various conditions in critically ill patients care such as septic shock[13] or acute respiratory distress syndrome.[14] It was demonstrated that a synergistic effect of these drugs improves the mortality and morbidity associated with these conditions.[11,12] Therefore, we considered that the addition of ascorbic acid and thiamine might confer a further beneficial effect to limit lung dysfunction caused by oxidative stress and inflammation in patients after esophagectomy treated with corticosteroids alone. On the basis of previously reported safety and potential benefits,[15] we began to use the combination of intravenous corticosteroids, ascorbic acid, and thiamine as adjunctive therapy for the intraoperative and postoperative management of patients undergoing esophagectomy. We conducted a retrospective before–after pilot study to evaluate impaired oxygenation in patients following esophagectomy comparing patients treated with intravenous corticosteroids, ascorbic acid, and thiamine and patients treated with corticosteroids alone.

Materials and Methods

Study design
This is a retrospective study, approved by the Institutional Review Board of Saiseikai Utsunomiya Hospital (No. 2018-14). Consecutive patients undergoing planned thoracoscopic esophagectomy for esophageal carcinoma between July and December 2018 were treated with a combination of corticosteroids, ascorbic acid, and thiamine in addition to standard postoperative management of patients after esophagectomy (corticosteroids were used routinely before this study).[16] Patients <20 years of age, those who received massive transfusions because of excessive intraoperative bleeding, conversion to open esophagectomy and those with limitations of care were not included in this study. The control group consisted of consecutive patients undergoing planned thoracoscopic esophagectomy between January 2016 and May 2018, using the same inclusion and exclusion criteria as the treatment group. The patients' clinical and demographic data were abstracted from the medical records.

Surgical procedure
All patients underwent thoracoscopic esophagectomy with lymphadenectomy and reconstruction with a gastric tube. During the intra-thoracic portion of the procedure, patients were placed in the left semi-prone position. Three 12-mm trocars and two 5-mm trocars were inserted. The right lung was deflated and gently displaced to the ventral side. Esophageal mobilization and mediastinal lymph node dissection were performed. After the intra-thoracic procedure, both recurrent laryngeal nerves, the aortic wall, left mediastinal pleura, pericardium, membranous portion of the trachea, and diaphragm were exposed in the surgical field. During the intra-abdominal portion, patients were placed in the supine position, and the mobilized esophagus was delivered through the enlarged hiatus. The stomach was prepared for reconstruction by dividing it at the cardia. This stage was performed through a laparotomy. In the cervical portion of the procedure, the cervical esophagus was mobilized using a collar incision, and the prepared gastric tube was pulled up through one of three routes: anterior sternal, retrosternal, or posterior mediastinal. The procedure was completed with a cervical esophagogastric anastomosis.

Perioperative management
All operations in this study were performed under general anesthesia with epidural analgesia. For standard prophylaxis against lung dysfunction following esophagectomy, methyl-prednisolone (125 mg/body)[8,17] was given at the beginning of the operation[16] and every 24 hours after the initial administration for 4 days (including the operative day). Postoperatively, all patients underwent mechanical ventilation and were cared for in the intensive care unit (ICU). In the ICU, all patients were treated according to a conservative, physiologically based fluid and vasopressor strategy,[18] and underwent mechanical ventilation with a lung-protective strategy (respiratory settings were initiated at low tidal volumes: 6 mL/kg, adequate positive end-expiratory pressure (5–10 cmH$_2$O) and fractional concentration of inspired oxygen (30%–40%), and were modified as oxygenation changed),[19] and limited use of sedation.[20] Patients received enteral nutrition via a jejunostomy tube started within 24 hours of surgery. Fluid administration was restricted after achieving of hemodynamic stability without vasopressors depending on oxygenation. After restricting fluids, if oxygenation was not

adequate, diuretics (furosemide, 40 mg/day) were given. Extubation was managed according to the Japanese protocol for liberation from mechanical ventilation,[21] when patients were physiologically stable, the ratio of the arterial partial pressure of oxygen (mmHg) to the fractional concentration of inspired oxygen (P_aO_2/F_iO_2 ratio) >300, and rapid shallow breathing index <80 /min/L, spontaneous breathing trial (SBT) was performed. SBT was performed with F_iO_2 30%, continuous positive airway pressure 5 cmH$_2$O and pressure support 5 cmH$_2$O. If the respiratory status of the patient did not deteriorate after an SBT, the patient was extubated.

Protocol for combined treatment with corticosteroids, ascorbic acid, and thiamine

Consecutive patients during the study period undergoing esophagectomy were given corticosteroids, ascorbic acid, and thiamine. Methyl-prednisolone was given as the corticosteroid with conventional dosing used for esophagectomy in Japan.[17] The protocol for ascorbic acid and thiamine used in this study was previously reported.[13] Thiamine was included in this protocol to assist in the metabolism of oxalate, a metabolite of ascorbic acid and may potentially cause kidney injury.[22] At the beginning of the operation, methyl-prednisolone (125 mg) was administered intravenously over 30 minutes. At the beginning of the intra-thoracic procedure, ascorbic acid (1.5 g) and thiamine (200 mg) were administered intravenously over 30 minutes. Methyl-prednisolone was given 125 mg every 24 hours postoperatively for 4 days (including the operative day), ascorbic acid was given 1.5 g every 6 hours after the initial administration for 4 days or until ICU discharge; thiamine was given 200 mg every 12 hours after the initial administration for 4 days or until ICU discharge.

Outcomes

The primary outcome of this study was oxygenation based on P_aO_2/F_iO_2 ratio during the first 2 days after surgery. In extubated patients, the F_iO_2 was estimated from settings of the oxygen delivery system.[23] Secondary outcomes were duration of mechanical ventilation and ICU stay, the rate of re-intubation, changes in white blood cell count, and serum concentration of C-reactive protein and postoperative complications.

Statistical analysis

All data are expressed as the mean ± standard error of the mean. The changes in P_aO_2/F_iO_2 ratio, white blood cell count, and serum C-reactive protein were analyzed using a mixed-effects model for repeated measures followed by a t-test for post hoc comparisons. The mixed-effects model for repeated measures included treatment group, time, and the treatment-by-time interaction as factors and a random intercept for each subject. Student's t-test and Fisher's exact test were used to test for differences in the remaining variables between the two groups. The differences were considered significant when the p value was <0.05. All of the data were analyzed using SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

There were six patients in the combination therapy group and 11 patients in the control group. Baseline characteristics are shown in **Table 1**, Operative and ICU data are presented in **Table 2**. There were no significant differences in baseline characteristics between the two groups. There were no significant differences in operative and ICU data between the two groups except for cumulative fluid balance and the use of diuretics in the ICU. In the control group, diuretics were used to decrease cumulative fluid balance to prepare for liberation from the ventilator.

Primary outcome
Oxygenation
Mean PaO_2/F_iO_2 ratios in the combination therapy group were significantly higher than those in the control group throughout the observation period (p <0.001). From the end of the operation, mean PaO_2/F_iO_2 ratios of the combination therapy group exceeded that of the control group (**Fig. 1**). The duration of mechanical ventilation was significantly shorter in the combination therapy group compared with the control group (combination therapy group vs control group, mean ± SEM: 2.0 ± 0.0 vs 4.2 ± 0.3 days, p <0.001). The rate of re-intubation in the combination therapy group was comparable to that in the control group (0 of 6 (0.0 %) vs 1 of 11 (9.1 %), p = 1.000) (**Table 3**). The ICU length of stay was shorter in the combination therapy group (3.2 ± 0.3 vs 6.9 ± 0.9 days, p = 0.009).

Secondary outcomes
Inflammatory response
There were no differences in the time course of white blood cell count or C-reactive protein level comparing the combination therapy group and the control group

Table 1   Patient characteristics

	Control (N = 11)	Combination therapy (N = 6)	p value
Age (years)	69.7 ± 2.3	67.7 ± 1.4	0.542
Body mass index (kg/m^2)	22.0 ± 0.7	21.1 ± 1.3	0.268
Male N (%)	10 (91)	4 (67)	0.515
Smoking history			0.600
Never	4 (36)	1 (17)	
Former	7 (64)	5 (83)	
Current	0 (0)	0 (0)	
Pack-years	31.5 ± 10.2	31.8 ± 8.2	0.985
ASA performance status			0.353
≤2	11 (100)	5 (83)	
≥3	0 (0)	1 (17)	
Tumor location			0.304
Ut	0 (0)	0 (0.0)	
Mt	5 (45)	5 (83)	
Lt	6 (55)	1 (17)	
Tumor stage			0.171
0/I	8 (73)	5 (83)	
II	3 (27)	0 (0)	
III	0 (0)	1 (17)	
Preoperative chemotherapy	7 (64)	2 (33)	0.335
Lung function			
Obstructive disorder (FEV1.0%<70%)	1 (9.1)	0 (0.0)	1.000
Restrictive disorder (%VC<80%)	0 (0.0)	0 (0.0)	1.000
Unknown	1 (9.1)	0 (0.0)	N.A

Values are expressed as the mean ± standard error of the mean or the number (percent). ASA: American Society of Anesthesiologists; FEV: forced expiratory volume; N.A: not available; Ut: upper; Mt: middle; Lt: lower

(**Fig. 2A** and **2B**). In both groups, the white blood cell count gradually increased over time. Although serum C-reactive protein levels in both groups at the end of surgery were comparable to the baseline values, the C-reactive protein level increased thereafter until the second postoperative day and decreased at the third postoperative day.

Postoperative complications
The incidence of postoperative complications was similar in the two groups. The rate of anastomotic leakage was 2/6 (33%) in the combination therapy group and 3/11 (27%) in the control group (p = 1.000). The incidence of acute respiratory distress syndrome, pneumonia, and recurrent nerve palsy, was similar in both groups (p = 1.000, p = 1.000, p = 0.600, respectively) (**Table 3**).

Discussion

In this study, we found that the perioperative administration of the combination of corticosteroids, ascorbic acid, and thiamine reduces the severity of impaired oxygenation after esophagectomy. Paul et al. reported that this combination was effective in preventing progressive organ dysfunction and in reducing the mortality of patients with septic shock.[13] To the best of our knowledge, this is the first report that the combination of corticosteroids, ascorbic acid, and thiamine reduces the severity pulmonary dysfunction after esophagectomy.

Impaired oxygenation after esophagectomy may be related to the systemic inflammatory response syndrome, which is invoked by tissue injury associated with surgery and one lung ventilation via inflammatory responses and oxidative stress.[4] This impairment is believed to begin intraoperatively and continue for several days.[24] Even after minimally invasive esophagectomy, which is less invasive than open esophagectomy, impaired oxygenation occurs and necessitates supportive care.[2] About 10% of patients who undergo thoracoscopic esophagectomy need prolonged mechanical ventilation and 7% of patients underwent unplanned intubation.[2] In the present study, the mean P_aO_2/F_iO_2 ratios in patients who received combination therapy are significantly higher than the control

Table 2 Operative and intensive care unit data

	Control (N = 11)	Combination therapy (N = 6)	p value
Operating time (min)	401 ± 14	407 ± 22	0.826
Duration of one lung ventilation (min)	209 ± 12	215 ± 12	0.739
Intraoperative blood loss	335 ± 95	546 ± 258	0.366
Reconstruction route			0.301
Anterior sternal	0 (0)	1 (17)	
Retrosternal	10 (91)	5 (83)	
Posterior mediastinal	1 (9)	0 (0)	
Intraoperative fluid given/weight	65.8 ± 4.5	70.9 ± 10.5	0.667
Intraoperative cumulative fluid balance/weight	50.3 ± 4.0	54.2 ± 8.5	0.636
Cumulative fluid balance/weight			
Postoperative day 1	82.1 ± 5.2	121.7 ± 17.8	0.013
Postoperative day 2	87.0 ± 9.2	137.5 ± 29.4	0.049
Medications given in the intensive care unit			
Vasopressors	2 (18)	2 (33)	0.584
Diuretics	7 (64)	0 (0)	0.035

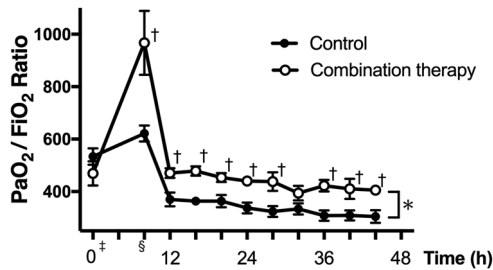Values are expressed as the mean ± standard error of the mean or the number (percent).

Fig. 1 Changes in P_aO_2/F_iO_2 ratios. The P_aO_2/F_iO_2 ratios were recorded from the beginning of surgery to 48 hours postoperatively. ‡: P_aO_2/F_iO_2 ratios recorded after intubation. §: P_aO_2/F_iO_2 ratios recorded at the end of operation (almost 8 hours after the beginning). The error bars show the standard error of the mean. * $p < 0.05$ indicates a statistically significant difference using a mixed-effects model for repeated measures. †$p < 0.05$ compared with the control group as determined by post-hoc analysis and Student's t-test.

Fig. 2 Changes in white blood cell count (**A**) and serum C-reactive protein levels (**B**). White blood cell count and C-reactive protein levels were recorded from the day before surgery as a baseline through the third postoperative day. The error bars show the standard error of the mean.

group throughout the observation period and all patients in the combined therapy group were extubated on the first postoperative day without subsequent re-intubation. The combination of corticosteroids, ascorbic acid, and thiamine appears to be effective in reducing the severity of lung dysfunction after esophagectomy.

Although ascorbic acid and corticosteroids have anti-oxidant and anti-inflammatory effects, respectively, it was suggested that the combination of these drugs is essential to produce a significant therapeutic effect.[25–28] It was reported that the efficacy of these drugs was seen in patients with
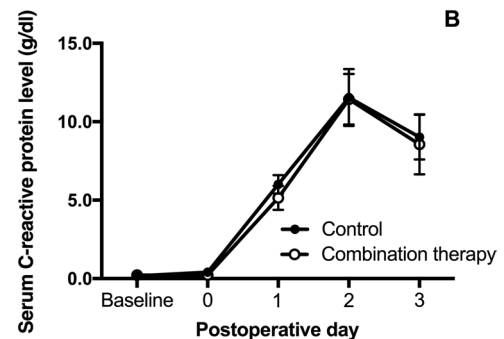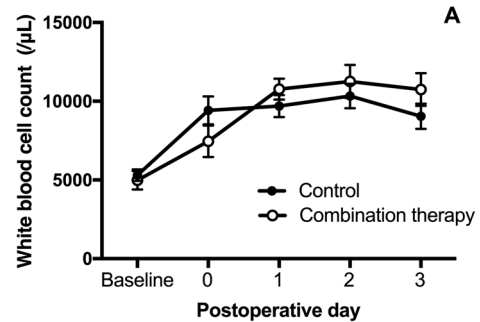
acute respiratory distress syndrome.[14] These drugs are believed to prevent and repair pulmonary endothelial barrier dysfunction or attenuate ischemia/reperfusion injury.[12,29] In patients undergoing esophagectomy, we

Table 3 Outcomes

	Control (N = 11)	Combination therapy (N = 6)	p value
Mechanical ventilation (days)	4.2 ± 0.3	2.0 ± 0.0	<0.001
Re-intubation	1 (9)	0 (0)	1.000
Tracheotomy	1 (9)	0 (0)	1.000
Intensive care unit length of stay (days)	6.9 ± 0.9	3.2 ± 0.3	0.009
Postoperative complications			
Acute respiratory distress syndrome	1 (9)	0 (0)	1.000
Anastomotic leakage	3 (27)	2 (33)	1.000
Pneumonia	5 (45)	2 (33)	1.000
Recurrent nerve palsy	4 (36)	1 (17)	0.600

The values are expressed as the mean ± standard error of the mean or the number (percent).

speculated that a similar mechanism is in effect to reduce surgically induced stress, resulting in improved oxygenation. We suggest that the combined treatment given acts at the level of pulmonary endothelial cells,[12] and does not result in elevation of the serum C-reactive protein level.

Cumulative fluid balance was significantly higher in the combined therapy group, which may be related to the use of diuretics and restricted fluid administration in the control group. To decrease cumulative fluid balance to improve oxygenation, diuretics were given to patients in the control group. Since the P_aO_2/F_iO_2 ratios in the combination therapy group were maintained postoperatively, the combined therapy group did not need diuretics and restricted fluid management to improve oxygenation. Excessive diuretic use and restricted fluid management may lead to renal dysfunction due to dehydration.[30] Diuretics also have a risk of inducing hypokalemia due to potassium excretion and sometimes, hyperkalemia due to excessive replacement. Avoiding the need for diuretics can avoid these risks in the postoperative period.

The safety of administering high-dose ascorbic acid has been reported.[22] High amounts of serum oxalate, a metabolite of ascorbic acid and normally excreted by the kidney, might have a risk for tissue deposition and crystallization in the kidney of patients with renal dysfunction if excessive amounts of ascorbic acid are given.[22] Thiamine helps oxalate metabolism, and a thiamine deficiency increases the conversion of glyoxylate to oxalate.[22] Therefore, thiamine was included along with high-dose ascorbic acid and corticosteroid combination therapy in these patients. The dose of ascorbic acid given was less than that in previous reports and did not cause adverse effects.[13]

This study has acknowledged limitations. It is a small, retrospective study and the two groups were not treated concurrently. This could have affected details of treatment, which could influence the outcomes. The results of this pilot study serve to support the conduct of a larger study, and possibly a randomized prospective trial in the future. The addition of ascorbic acid is associated with low risk at low cost.

Conclusion

The results of the present study suggest that combined therapy with corticosteroids, ascorbic acid, and thiamin may be effective in reducing the severity of impaired oxygenation following esophagectomy. Although this small pilot retrospective study has limitations, this safe and inexpensive combination therapy has the potential to improve P_aO_2/F_iO_2 ratios after esophagectomy. Additional large-scale prospective studies are required to confirm these preliminary findings.

Disclosure Statement

None.

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