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Propofol for Anesthesia and Postoperative Sedation Resulted in Fewer Inflammatory Responses than Sevoflurane Anesthesia and Midazolam Sedation after Thoracoabdominal Esophagectomy

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ABSTRACT

Responses to surgical stress can be modulated by anesthetics. We prospectively compared the effects of two different anesthetic/sedative techniques on the peak postoperative bladder temperature (BT) and the postoperative C-reactive protein (CRP) level. Twenty patients who were scheduled to undergo elective thoracoabdominal esophagectomy were allocated to receive either propofol anesthesia followed by propofol sedation (PP group, n = 10) or sevoflurane anesthesia followed by midazolam sedation (SM group, n = 10). In each case, the patient's peak bladder temperature was measured on the morning after surgery, and their serum CRP levels were assessed on postoperative days (POD) 1, 2, and 3. The patients' postoperative clinical courses were also evaluated. The peak postoperative BT (°C) (37.6 ± 0.4 vs. 38.2 ± 0.6, respectively; $p < 0.05$) and the CRP level on POD 2 (mg/dl) (14.3 ± 3.9 vs. 20.6 ± 3.9, respectively; $p < 0.05$) were lower in the PP group than in the SM group. The peak postoperative BT was positively correlated with the CRP level on POD 2 ($R = 0.533$, $p < 0.05$). There were no significant differences between the clinical course-related parameters in both groups. Propofol anesthesia and postoperative propofol sedation resulted in a reduced peak postoperative BT and lower CRP levels on POD 2 after esophagectomy than sevoflurane anesthesia followed by midazolam sedation.

Key words: *Inflammatory response, Propofol, Sevoflurane, Midazolam*

Thoracoabdominal esophagectomy, which is one of the most invasive surgical procedures, often causes postoperative fever and high C-reactive protein (CRP) level. Both of these symptoms are frequently used as indicators of the inflammatory response at the bedside. A recent report showed that fever was independently associated with mortality in non-septic patients including those who have undergone surgery[17]. The CRP level is markedly increased by surgical procedures. The more invasive the surgical procedure, the more the CRP level increases[10, 28]. In addition, the CRP levels on postoperative days (POD) 2-4 have proven to be useful for predicting postoperative complications[1, 18, 23].

The anti-inflammatory effects of propofol have been compared with those of other anesthetics in previous studies. Several studies have demonstrated that propofol attenuates the production of pro-inflammatory cytokines more effectively than sevoflurane or midazolam[8, 14, 31]. Hence, the infusion of propofol during or after surgery might result in smaller postoperative increases in the patient's body temperature and CRP level compared with the inhalation of sevoflurane or the infusion of midazolam. However, to the best of our knowledge, no previous studies have compared the effects of propofol on patients' postoperative body temperature or CRP level with those of other anesthetics.

The aim of the present study was to examine the postoperative body temperature and CRP level of patients who underwent thoracoabdominal esophagectomy and to compare these parameters between patients who were subjected to propofol anesthesia followed by postoperative propofol sedation and those who were subjected to sevoflurane anesthesia followed by postoperative midazolam sedation. In addition, various clinical course-related parameters were compared between the two groups.

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SUBJECTS AND METHODS

The protocol of this study was approved by the ethics committee of Hiroshima University Hospital (No.: 40006) and registered in the Universal Hospital Medical Information Network Clinical Trials Registry (ID: UMIN000009023, http://www.umin.ac.jp/ctr). Informed consent was obtained from all participating patients. The preoperative exclusion criteria included a body mass index (BMI) of >30 kg/m^2; a history of diabetes mellitus, hyperlipidemia, or renal dysfunction (creatinine >1.0 mg/dl); having received a high calorie infusion or chemoradiotherapy within a month of surgery; or being administered steroids or non-steroidal anti-inflammatory drugs (NSAID). A total of 24 male cancer patients with American Society of Anesthesiologists Physical Status classifications of I or II who underwent elective thoracoabdominal esophagectomy and gastric tube reconstruction without laparoscopy at 9:00 am were enrolled into this prospective study. All started fasting at midnight on the day of surgery, and no preanesthetic medications were administered in any case.

The patients were divided into two groups using pre-prepared sealed envelopes: the propofol anesthesia followed by propofol sedation group (PP group) and the sevoflurane anesthesia followed by midazolam sedation group (SM group). The primary outcome variable was the postoperative peak bladder temperature (BT), which was measured early in the morning after the procedure. The secondary outcome variables included the postoperative CRP level; skinfold measurements obtained with skinfold calipers; and parameters related to the patients' clinical courses, including the number of anastomotic leaks, the number of times reintubation was required, the time until oral intake was re-initiated, and length of the hospitalization period.

Sample size was determined based on the authors' preliminary data about the peak postoperative BT of patients that underwent thoracoabdominal esophagectomy. The expected inter-group difference in peak BT was 0.657°C [standard deviation, 0.49]. It was estimated that a sample size of 10 subjects in each group would provide an α value of 0.05 and 80% power for detecting such inter-group differences.

Anesthesia and intensive care management

In both groups, an arterial line was inserted into the left radial artery before the induction of anesthesia to enable repeated blood sampling and continuous blood pressure monitoring. In the PP group, anesthesia was induced via a target-controlled infusion of 3.0 μg/ml propofol and 2.0 μg/kg of fentanyl and was maintained with propofol and fentanyl. In the SM group, anesthesia was induced with 3.0-5.0 mg/kg thiamylal and 2.0 μg/kg fentanyl and was maintained with sevoflurane and fentanyl. The dosage of propofol or sevoflurane was adjusted according to the bispectral index (A-2000 monitor™; Aspect Medical Systems, Newton, MA, USA). Fentanyl was repeatedly administered at intravenous doses ranging from 25-100 μg. In addition, 250 mg methylprednisolone were given just before surgery. During surgery, the infusion rate of glucose-free Ringer's acetate solution was adjusted to ensure that the patients' urinary output remained above 0.5 ml/kg/hr, and 5% glucose acetate maintenance solution was infused at a rate of 50 ml/hr. The patients' blood pressure and heart rate were maintained within 25% of their preoperative values. Dopamine was administered intravenously when necessary. The temperature of the operation room was maintained at between 22 and 24°C. A warming system (WarmTouch™, Covidien, Mansfield, MA, USA) was used to maintain the patients' BT (which was measured with a Bardex Lubricath Temperature-Sensing Foley Catheter™; C. R. Bard, Murray Hill, NJ, USA) within the normal range (36-37°C).

After the procedure, the patients were transferred to the intensive care unit (ICU) and were placed on mechanical ventilation until postoperative day (POD) 3. Sedation was maintained with propofol in the PP group and with midazolam in the SM group with the aim of achieving a Ramsey sedation score[25] of between 3 and 4. The postoperative pain management strategy involved the nurse-controlled intravenous administration of 25 μg/ml fentanyl (dose: 2 ml/hr for basic infusions; 1 ml for bolus injections; lock-out time: 5 min). Postoperatively, the patients received 4.3% glucose acetate maintenance solution at a rate of 100 ml/hr until 10:00 am on POD 2, followed by a high-calorie infusion containing 560 kcal/903 ml, which was delivered at a rate of 60 ml/hr. The infusion rate of Ringer's acetate solution was adjusted (between 0 and 200 ml/hr) to ensure that the patients' urinary output remained above 0.5 ml/kg/hr. The temperature of the ICU was maintained within 25 ± 0.5°C.

Measurements

The measurement protocol employed in the operation room and ICU is shown in Fig. 1. On the basis of our preliminary data, we predicted that the patients' BT would peak around 6 hr after surgery. Thus, we recorded the patients' BT every 2 hr until 14 postoperative hours using the Perioperative Information Management System (PIMS™; Royal Philips Electronics, Amsterdam, Noord-Holland, NLD) in the ICU. Blood samples were obtained before and after surgery and used to determine the patients' serum CRP, triglyceride, glucose and leptin levels. Energy expenditure (EE) and the respiratory quotient (RQ) were assessed using indirect calorimetry (Vmax29n™; VIASYS Respiratory Care, Yorba Linda, CA, USA) at the same time as the blood sampling (except before the operation).

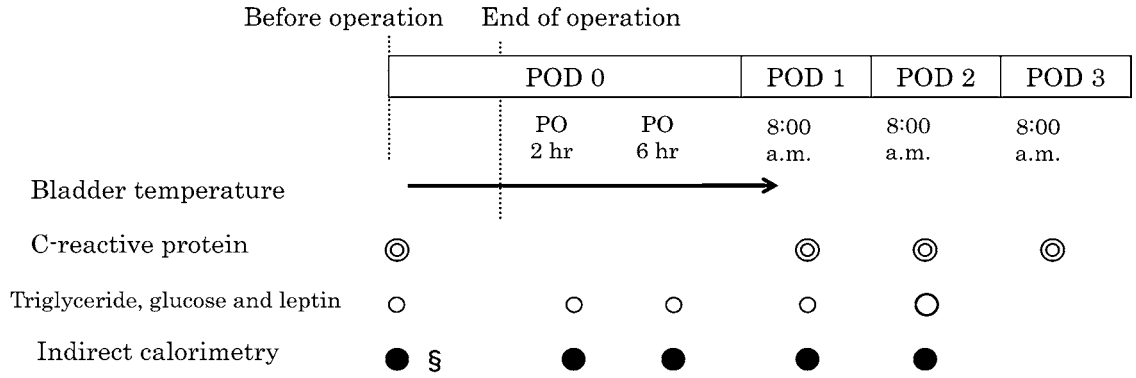

Fig. 1. Schematic diagram of the measurement protocol employed in the operation room and intensive care unit
PO: postoperative, POD: postoperative day, hr: hours.
§ Predicted resting energy expenditure according to the Harris-Benedict equation was used as a substitute for energy expenditure according to indirect calorimetry.

Preoperative predicted basal energy expenditure (kcal/day) was calculated according to the Harris-Benedict equation: 66.47 + 13.75 × body weight (kg) + 5.003 × height (cm) + 6.775 × age (years).

According to the methods described by Bishop et al[2], arm circumference (AC, cm) and triceps skinfold measurements (TSF, mm; an indicator of subcutaneous fat mass) were obtained using skinfold calipers (ADIPOMETER™; Abbott Japan, Mita, Tokyo, JPN) and a tape measure on the day before surgery and on POD 18 (the day the patients were discharged from hospital if they were free from complications). Arm muscle circumference (AMC), an indicator of skeletal muscle mass, was calculated from AC and TSF using the following equation: AMC = AC (cm) − 3.14 × TSF (mm) × 1/10. To reduce error, all of the AC and TSF measurements were performed by the same observer. Five measurements were taken, and the mean of the three middle values was used. Furthermore, %TSF was calculated using the following equation: %TSF = (TSF on POD 18) / (TSF on the day before surgery) × 100 (%). %AC and %AMC were calculated using similar equations.

The number of anastomotic leaks, the number of times reintubation was required, the time until oral intake was reinitiated, and the length of the postoperative hospitalization period were also recorded.

Statistical analysis

Data are expressed as mean ± SD values for parametric data or median (range) values for non-parametric data. Inter-group differences in individual variables were evaluated using Student's t-test, Fisher's exact test, or Mann-Whitney U-test, as appropriate. Tukey-Kramer test was used to correct for multiple comparisons. The correlations between peak postoperative BT and the CRP level or between peak postoperative BT and %TSF were analyzed using Pearson's product-moment correlation method. p-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with StatView 5.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A CONSORT flow diagram is shown in Fig. 2. Twenty-four patients had their eligibility for this study assessed. Four of them met one or more of the exclusion criteria, and so the remaining 20 patients took part in the study; thus, both groups consisted of 10 patients. The patients' preoperative and intraoperative data are summarized in Tables 1 and 2, respectively. In the PP group, the intraoperative and postoperative propofol doses were 5.2 ± 0.8 mg/kg/hr and 73 ± 20 mg/kg/day, respectively. In the SM group, the postoperative midazolam dose was 2.8 ± 0.8 mg/kg/day. None of the patients required NSAID, beta-adrenergic antagonists, insulin, diuretics, or dopamine >3 μg/kg/min during their stay in the ICU.

At 6, 8, and 10 hr after surgery, the mean BT of the PP group was significantly lower than that of the SM group (Fig. 3). The peak postoperative BT of the PP group was also significantly lower than that of the SM group (37.6 ± 0.4°C vs. 38.2 ± 0.6°C, $p = 0.014$). The PP group exhibited a significantly lower CRP level than the SM group on POD 2 (Fig. 4). Conversely, %TSF was significantly higher in the PP group (Table 3). Peak postoperative BT was positively correlated with the CRP level on POD 2 ($R = 0.533$, $p = 0.014$) and negatively correlated with %TSF ($R = 0.475$, $p = 0.033$). None of the other clinical course-related parameters differed significantly between the two groups (Table 3). However, two patients in the SM group, whose temperatures became lower than 38°C on POD 2 in the same course as the other patients', suffered anastomotic leaks which were diagnosed on POD 6 or later. Even after the exclusion of these patients' data, the inter-group differences in peak postoper-

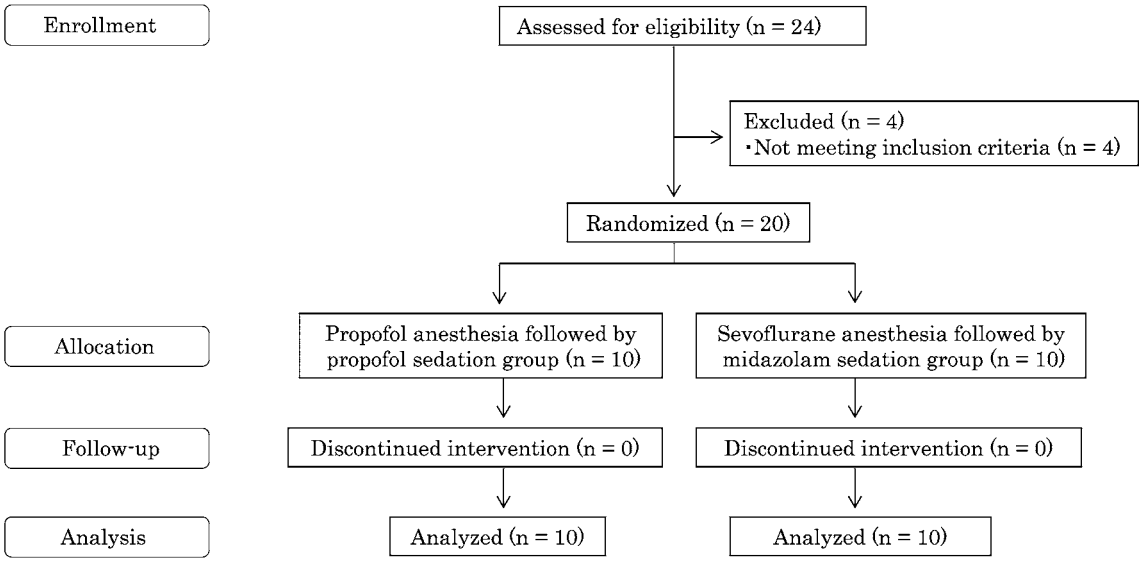

Fig. 2. CONSORT flow diagram for the study enrollment

Table 1. Demographic data before surgery

	PP group (n = 10)	SM group (n = 10)
Age (years)	62 ± 10	67 ± 8
Height (cm)	165 ± 6	162 ± 6
Weight (kg)	67 ± 14	62 ± 8
Body mass index (kg/m^2)	24.0 ± 3.9	23.5 ± 3.0
Arm circumference (cm)	25.9 ± 3.1	25.3 ± 2.2
Arm muscle circumference (cm)	23.4 ± 1.8	22.4 ± 1.6
Triceps skinfold thickness (mm)	8.2 ± 4.7	9.4 ± 4.8
pREE (kcal/m^2/day)	798 ± 55	768 ± 46
Blood urea nitrogen (mg/dl)	13.3 ± 2.7	13.1 ± 3.0
Creatinine (mg/dl)	0.76 ± 0.11	0.83 ± 0.11
Hematocrit (%)	39 ± 4	37 ± 5
Albumin (g/dl)	4.0 ± 0.4	4.2 ± 0.4
Neoadjuvant chemoradiotherapy (n)	4	3
Stage (0/ I/ II/ III/ IV) (n)	2/ 3/ 2/ 3/ 0	0/ 5/ 3/ 1/ 1

Data are expressed as mean ± SD values for quantitative variables or as n values for qualitative variables. No significant differences were detected between the groups pREE (kcal/day): Predicted resting energy expenditure according to the Harris-Benedict equation; i.e., 66.47 + 13.75 × body weight (kg) + 5.003 × height (cm) + 6.775 × age (years)

Table 2. Demographic data during surgery

	PP group (n = 10)	SM group (n = 10)
Operative duration (hr)	7.0 ± 1.2	6.9 ± 1.5
Duration of anesthesia (hr)	8.7 ± 1.2	8.5 ± 1.6
Blood loss (ml)	809 ± 718	585 ± 424
Intravenous fluid volume (ml/kg/hr)	6.9 ± 1.5	7.7 ± 1.9
Glucose dose (mg/kg/hr)	49 ± 15	57 ± 17
Fentanyl dose (μg/kg/hr)	5.1 ± 1.5	5.4 ± 1.7
Urinary output (ml/kg/hr)	1.3 ± 0.9	1.1 ± 0.6
Dopamine agonist treatment (n)	5	5
Lymph node dissection type (two-field : three-field)	7 : 3	6 : 3*

Data are expressed as mean ± SD values for quantitative variables or as n values for qualitative variables.
No significant differences were detected between the groups
*One patient in this group did not undergo lymph node dissection

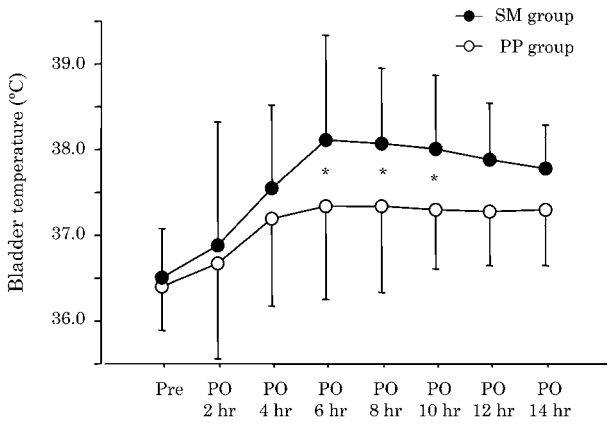

Fig. 3. Changes in bladder temperature until 14 postoperative hours in the SM and PP groups
Data are expressed as mean ± SD values.
Pre: preoperative measurement, PO: postoperative, hr: hours.
*p <0.05, significant difference between the groups.

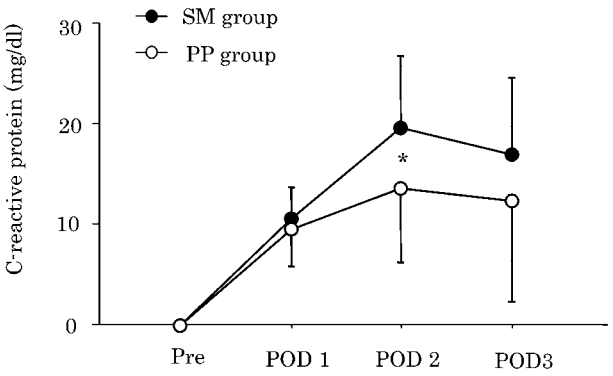

Fig. 4. Changes in C-reactive protein levels after surgery in the SM and PP groups Data are expressed as mean ± SD values.
Pre: preoperative measurement, POD: postoperative day.
*p <0.05, significant difference between the groups.

Table 3. Secondary outcomes excluding CRP levels

	PP group (n = 10)	SM group (n = 10)
% AC (%)	95.1 ± 5.2	94.0 ± 2.7
% AMC (%)	95.5 ± 5.1	95.5 ± 3.4
% TSF (%)	86.9 ± 8.2	75.2 ± 11.5*
Anastomotic leakage (n)	0	2
Reintubation (n)	0	1
Time to reinitiation of oral intake (days)	9.5 (8-19)	10 (8-60)
Length of hospital stay (days)	19 (18-26)	19 (18-88)

Data are expressed as mean ± SD, n, or median (range) values.
AC: arm circumference, AMC: arm muscle circumference, TSF: triceps skinfold measurement
* Significantly different from PP group, p <0.05

ative BT (37.6 ± 0.4°C vs. 38.1 ± 0.7°C, p <0.05), the CRP level on POD 2 (14.3 ± 3.9 mg/dl vs. 20.4 ± 4.0 mg/dl, p <0.05), and %TSF (86.9 ± 8.2% vs. 77.3 ± 6.5%, p <0.05) remained significant.

No differences in EE, the RQ, or the levels of triglycerides, glucose, or leptin were detected at any time point (data not shown).

DISCUSSION

In this study, peak postoperative BT and the serum CRP level on POD 2 were significantly lower in the PP group than in the SM group. In addition, peak postoperative BT was correlated with the CRP level on POD 2. However, there were no differences between the clinical course-related parameters of the two groups. Several studies have suggested that patients' clinical courses after esophagectomy can be improved by preventing excessive surgical inflammation[6,9,11,22,29]. In another report, fever was found to be independently associated with mortality in non-septic patients, including those who had undergone surgery[17].

No previous studies have detected differences between the effects of propofol and other anesthetics on both postoperative body temperature and CRP level. Among several representative pro-inflammatory cytokines, interleukin 6 (IL-6) is known to be a major perioperative pyrogen[4] and an important regulator of acute phase protein production, including CRP production[12]. A systematic review showed that the timing of the peak postoperative CRP level occurred later than that of IL-6, between 24 and 72 hr after major procedures[30]. Although we did not measure the patients' IL-6 level in this study, peak postoperative BT was positively correlated with the CRP level on POD 2. Taking the above points into account, our results suggest that pro-inflammatory cytokine production, especially IL-6 production, might be lower in the PP group than in the SM group. Two previous studies have compared the effects of propofol and sevoflurane anesthesia on the intraoperative IL-6 level. In these studies, it was found that propofol attenuated the increase in the IL-6 level caused by surgery more effectively than sevoflurane. Specifically, these effects were observed prior to the initiation of cardio-

pulmonary bypass[8] and before and after one-lung ventilation during lobectomy[14]. However, a report showed that sevoflurane attenuated the increase in IL-6 and CRP levels after lung lobectomy more effectively than propofol[24]. Furthermore, other studies found that there was no difference between the anti-inflammatory effects of propofol and sevoflurane anesthesia during open colorectal surgery or lung lobectomy[15, 16]. Therefore, it is controversial whether propofol has more effective anti-inflammatory potential than sevoflurane. On the other hand, Xia et al showed that propofol attenuated the increase in the IL-6 level induced by surgery more effectively than midazolam 2 hr after the release of aortic cross-clamps as well as 24 hr after cardiac surgery[31]. They concluded that propofol had greater potential to reduce inflammation than midazolam. Therefore, we speculate that the significant inter-group differences in peak postoperative BT and the CRP level on POD 2 observed in the present study might be attributable to the different anesthetics used for sedation rather than to anesthesia.

In the present study, %TSF, an indicator of subcutaneous fat mass, was significantly higher in the PP group than in the SM group. Thus, the infusion of propofol might be associated with a reduction in endogenous lipid recruitment. Since propofol is formulated as an emulsion containing about 10% triglycerides[21], propofol infusions might attenuate fat hypercatabolism by supplying fat during the perioperative period, when fat metabolism is considered to be increased[27]. However, we could not find any evidence that the triglycerides in the propofol emulsion affected perioperative fat metabolism because no significant differences in the RQ or triglyceride levels were detected between the two groups. Fat catabolism is mediated by changes in hormonal and sympathetic nervous system activity caused by surgical stress, e.g., increases in epinephrine, cortisol, and sympathetic activity accelerate lipolysis[5, 7]. Some studies have demonstrated that propofol attenuates the increases in epinephrine and cortisol levels induced by surgery more effectively than sevoflurane[19, 20] and depresses sympathetic activity more effectively than midazolam[13]. Hence, these effects of propofol on perioperative hormonal and sympathetic activity might also be associated with changes in %TSF. However, many other factors affect fat catabolism, including nutritional management, adipokines and hormones such as insulin and growth hormone[5, 26]. Therefore, we cannot definitively state that the two anesthetic/sedative techniques directly influenced %TSF, although %TSF was weakly correlated with peak postoperative BT.

The mean dose of propofol for postoperative sedation was 73 mg/kg/day in this study, which was slightly over maximal recommended doses of 3.0 mg/kg/hr in the Japanese drug package insert. However, in a supplementary comment, it is stated that the dose of propofol should be increased or decreased according to the status of patients on clinical necessity. The dose of propofol seemed not to be excessive as it was needed as a clinical requirement.

Limitations

The present study had several limitations. First, we did not measure the patients' IL-6 levels. As a result, we could not definitively determine whether the differences between the peak postoperative BT and the CRP level of the two groups were attributable to the anti-inflammatory effects of propofol. Second, the data for the SM group included data for two patients who suffered anastomotic leaks. When we re-analyzed the data after excluding these patients, the differences in peak postoperative BT, the CRP level on POD 2, and %TSF remained significant. Therefore, we consider that our findings regarding the differences between the groups are valid. Third, ideally we should have set up another group in which the patients were given an intravenous infusion containing an equivalent amount of triglycerides to that found in propofol to investigate the effects of triglycerides on the peak postoperative BT, the CRP level, and %TSF. However, it has been suggested that the use of triglyceride infusions during surgery can cause liver dysfunction or fatty liver[3]. Therefore, we did not include such a group due to ethical considerations.

In summary, among patients who underwent thoracoabdominal esophagectomy the peak postoperative BT and the CRP level on POD 2 were lower in the PP group than in the SM group. Further studies of the effects of different anesthetic/sedative techniques on inflammatory responses are needed.

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