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Original Article

Effects of Sevoflurane and Propofol on Intestinal Ischemic Reperfusion Injury in Patients Undergoing Elective Open Infrarenal Abdominal Aortic Aneurysm Repair: A Randomized Controlled Trial

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ABSTRACT

Background: We previously demonstrated that propofol had a protective effect on the intestine at risk after an ischemic injury in a rat model. The current study tested the hypothesis that such beneficial effects, so far mainly seen in the laboratory, are reproducible in humans.

Methods: Seventy patients undergoing elective open infrarenal abdominal aortic aneurysm repair were randomized to receive general anesthesia with either propofol or sevoflurane. General anesthesia was induced with 3 μg/kg fentanyl, 0.2 mg/kg cisatracurium, and target-controlled infusion of propofol, set at a plasma target concentration of 4-6 μg/ml, or sevoflurane initially started at 8%. Anesthesia was maintained with target-controlled infusion of propofol (2-4 μg/ml) or sevoflurane (0.8-1.0 minimum alveolar concentration). Except for this, anesthetic and surgical management was the same in both groups. Serum intestinal fatty acid binding protein was taken as the primary outcome for evaluating intestinal injury. The secondary outcomes included other intestinal injury variables (serum endotoxin levels, serum diamine oxidase activity and the score of intestinal injury severity) as well as markers reflecting oxidative stress and systemic inflammatory response.

Results: The levels of biomarkers reflecting intestinal injury were higher than baseline in both groups (all $P<0.05$). However, in sevoflurane- anesthetized patients, these variables increased significantly more than those in patients anesthetized with propofol (all $P<0.05$), whereas the scores of the intestinal injury severity didn't differ between two groups ($P=0.53$).

Conclusions: Patients receiving propofol for abdominal aortic aneurysm repair surgery had less intestinal injury than patients receiving sevoflurane, which may be related to its better anti-oxidative property.

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Intestinal ischemia/reperfusion (I/R) injury may occur after acute mesenteric ischemia, traumatic or septic shock, hemorrhagic or some surgical procedures including small bowel transplantation and abdominal aortic surgery (1). It not only leads to injury of the intestine itself, but also subsequently results in the translocations of bacteria and endotoxin across intestinal mucosal barrier, leading to the systemic releases of reactive oxygen species (ROS) and inflammatory cytokines with subsequent multiple organ dysfunction syndrome (MODS) (2, 3).

Propofol is an intravenous anesthetic with antioxidant properties that is commonly used for the induction and maintenance of anesthesia during surgery and for postoperative sedation in intensive care unit (ICU) (4-8). We have recently demonstrated that pretreatment with propofol attenuates intestinal mucosal injury induced by intestinal I/R in rats, which is attributable to its antioxidant properties and the effects in inhibiting over-production of nitric oxide and decreasing endothelin- 1 level (9). Further, we found that the intestinal protective effect of propofol involves the attenuation of intestinal I/R- induced intestinal epithelial apoptosis via modulating the ceramide signaling pathway (10). However, whether such beneficial effects, so far mainly seen in the laboratory, are reproducible in human remains unclear.

Open abdominal aortic aneurysm (AAA) repair still is a good alternative for some special patients. However, it is known that open AAA repair causes significant morbidity and mortality and postoperative MODS is a major cause (11, 12). Since the procedure usually involves clamping and unclamping of aorta and inferior mesenteric artery, it is postulated that I/R injury of the intestine could be the leading cause for MODS (13, 14).

Thus, we hypothesized that the intestinal protective effect of propofol seen in the laboratory is reproducible in humans and thereby selected patients undergoing elective open infrarenal AAA repair as a clinical model of intestinal I/R injury to investigate the intestinal protective potential of propofol. Meanwhile, sevoflurane, a commonly used halogenated volatile anesthetic which has been demonstrated to induce myocardial protection (15, 16), was taken as a control to determine which anesthetic regimen would lead to a better protection against intestinal I/R injury induced by open infrarenal AAA repair.

Intestinal protection was assessed by the serum level of intestinal fatty acid binding protein (I- FABP), a sensitive marker of early intestinal ischemia (17), which was considered the primary outcome variable, endotoxin level and the diamine oxidase (DAO) activity in serum as well as a modified intestinal dysfunction score based on previously described methods (18). Markers of systemic inflammation and oxidative stress were determined as well.

MATERIALS AND METHODS

Protocols and Ethics

The study protocol was conducted in accordance with the Helsinki declaration (2008) and approved by the Research Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University, China.

Before the trial, enrolled patients were randomized into a sevoflurane group or a propofol group. Randomized treatment allocations with no further stratification were generated using a computer random number generator with a 1:1 allocation using blocks of varying sizes. Allocation details were placed in sequentially numbered sealed envelopes. To standardize technical skills and experience, every case was performed by the same anesthesiologists and surgeons. Treatment allocation was revealed by anesthesiologists on the morning of surgery and supervised by an independent statistician. None of the anesthesiologists participated in the data assessment or analysis. Patients, investigators, surgeons, critical care teams and individuals participating in data analysis were all blind to group allocation. The trial was monitored by an independent data and safety monitoring board. Group allocation was not revealed until the final statistical analysis was completed.

Patients

A prospective, single- blind, randomized controlled trial following the CONSORT statement was conducted on patients undergoing elective open infrarenal AAA repair. Written informed consent was obtained from each participant. In-

clusion criteria were age greater than 18 years, elective open infrarenal AAA repair surgery and American Society of Anesthesiologists (ASA) physical status III or less. Exclusion criteria included patients older than 80 years, a history of allergy to propofol, previous cardiac surgery, combined surgery, myocardial infarction within the previous 6 weeks, severe chronic obstructive pulmonary disease (forced expiratory volume in 1 second, FEV1<50%), severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >150 U/L), renal failure (creatinine concentration >150 μmol/L), preoperative antioxidant therapy and pregnancy, history of inflammatory bowel disease, history of diarrhea (≥ 2 liquid stools/day for ≥2 days) within 1 week of surgery and intestinal chronic inflammatory disease. Additionally, Glasgow Aneurysm Score was assessed for each patient before operation in order to ensure that operative risk between groups was similar (19).

Anesthesia and Surgical Procedure

No premedication was given before anesthesia. Routine monitoring for open infrarenal AAA repair surgery included electrocardiograph (ECG), pulse oximetry, capnography, temperature, arterial blood pressure, central venous pressure (CVP) and urine output.

All patients underwent general anesthesia combined with epidural anesthesia. Before induction of general anesthesia, a thoracic epidural catheter was inserted between the T12-L1 or L1-L2 level using a midline or paramedian approach in all patients, through which a test dose of 5 ml of 1% lidocaine was given. After 15 minutes, the quality of the epidural analgesia was assessed using cold discrimination. If pain relief was inadequate, the position of the epidural catheter was adjusted or a new catheter was placed if necessary. The anesthesia staff was instructed not to use the epidural catheters intraoperatively.

In the sevoflurane group, anesthesia was induced with sevoflurane (Sevorane®, Abbott Scandinavia AB, Solna, Sweden) initially started at 8% by deep breathing, followed by 0.2 mg/kg cisatracurium and 3 μg/kg fentanyl. Anesthesia was maintained with sevoflurane 0.8-1.0 minimum alveolar concentration and remifentanil 0.2-0.4 μg/kg/minute. In the propofol group, general anesthesia was induced with a target-controlled infusion of propofol (Diprifusor; AstraZeneca S.p.A, Milan, Italy), set at a plasma target concentration of 3-5 μg/ml, followed by 0.2 mg/kg cisatracurium and 3 μg/kg fentanyl. Anesthesia was maintained with propofol at target concentrations of 2-4 μg/ml and remifentanil 0.2-0.4 μg/kg/minute. Depth of anesthesia was determined with the bispectral index (BIS) (BIS Vista, Aspect Medical Systems, Norwood, MA, USA) with a target range between 40 and 50 during surgery. Cisatracurium was administered for further muscle relaxation, as clinically indicated in two groups. Patients were intubated with a 7.5 mm cuffed endotracheal tube and the ventilation parameters were standardized (respiratory rate 12-15 breaths/minute, tidal volume 8-10 ml/kg, fraction of inspired oxygen 1.0) to achieve 35-45 mm Hg of end-tidal carbon dioxide concentration ($ETCO_2$). Standardized fluid replacement consisted of 10 ml/kg lactated Ringer's solution applied preoperatively and 6 ml/kg/hour of the solution applied perioperatively. Colloid was given to obtain a stable heart rate, CVP of 8-10 cm H_2O, a steady mean arterial pressure (MAP) and a urine output >1 ml/kg/hour. Packed red cells were transfused as necessary to maintain a circulating hemoglobin level approximately 8 g/dl. Hemodynamic management was standardized to maintain a steady MAP by inotropic and vasodilator therapy.

Postoperative Management

At the end of surgery, the patients were routinely transferred to ICU, and all patients received the same routine postoperative care. The epidural catheter infusions were begun immediately upon entry to ICU. The loading dose was 6 ml of 0.25% bupivacaine with 2 mg morphine and during the first 3 postoperative days, all patients received epidural analgesia with a mixture of bupivacaine 0.125% and 0.1 mg/ml morphine with a basal rate of 2 ml/hour, bolus doses of 3-5 ml, and a lockout interval of 20 minutes. To make sure that those patients had a working epidural analgesia, postoperative pain was assessed at rest and movement during postoperative days 1, 2, and 3 by using the visual analog scale rating from 0 (no pain at all) to 10 (worst possible

pain). In ICU, crystalloid fluid replacement was infused at 2 ml/kg/hour to maintain a stable heart rate, CVP of 8-10 cm H_2O and a steady MAP. Also, blood was given to maintain hemoglobin more than 8 g/dl. Extubation was managed according to the standard ICU protocols by the ICU staff.

The Preparation of Blood Sampling

Blood samples were collected for analysis at the following time points: before the start of surgery (baseline), 30 minutes, 4, 8, 12, and 24 hours after cross-clamping release (reperfusion). Venous blood was sampled from the jugular venous line and centrifuged at 2700 rpm for 15 minutes. Serum samples were stored at -70° C for subsequent analysis. Radial arterial blood was analyzed using a GEM premier 3000 blood gas system (GEM Premier 3000, Instrumentation Laboratory, Bedford, MA, USA).

Assessment of Intestinal Injury

Intestinal injury was assessed by measuring the serum concentrations of I-FABP and endotoxin, as well as the activity of DAO at predetermined time points. The concentration of I-FABP was measured by enzyme-linked immunosorbent assay according to the instruction manual (ADL Co, Mukwonago, WI, USA). The concentration of endotoxin was determined using a quantitative Limulus amoebocyte lysate (LAL) chromogenic assay (Ruicheng Bio-engineering Research Institute, Shanghai, China). DAO activity was assessed using a sandwich enzyme-linked immunoassay with a commercially available kit (HuiJia Bio-engineering Research Institute, Xiamen, China).

To evaluate the patients' intestinal function after aneurysm repair, a modified intestinal dysfunction score based on previously described methods (19) was used. Since patients usually start enteral feeding from the third day after AAA surgery in our center, the recording of intestinal injury score was initiated from 72 hours after operation.

Evaluation of Inflammatory Response and Oxidative Stress

The levels of the inflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) were measured using a sandwich enzyme-linked immunoassay with a commercially available kit (Jiancheng Bio-engineering Research Institute, Nanjing, China). The variables reflecting oxidative stress including malondialdehyde level and superoxide dismutase (SOD) activity in serum were analyzed using methods of thiobarbituric acid reaction and the generation of an artificial chromophore, respectively.

Statistical Analysis

Serum I-FABP concentration served as the primary outcome variable. Sample size was calculated based on differences in I-FABP concentration measured at 30 minutes after cross-clamping release in a pilot study of 10 patients who received either propofol anesthesia (204.0 ± 21.1 pg/ml) and sevoflurane anesthesia (230.1 ± 36.3 pg/ml). The formula $N=15.7/ES^2+1$, wherein ES is the effect size= (difference between groups)/ (mean of the standard deviation [SD] between groups), with $\alpha=0.05$ and power=0.8 was used to determine that the study required N of 33 per group (20). However, in order to compensate for a 10% of drop-out rate during study period, 70 patients were recruited in this study.

Continuous data were expressed as means ± SD, or median (25% percentile, 75% percentile) of patients and compared with independent *t* test or Mann-Whitney *U* test, respectively. Categorical data were expressed as frequency or percentage and compared with Fisher's exact test or the chi-square test where appropriate. The severity of intestinal injury was compared by the Mann-Whitney *U* test. The hemodynamic data and biochemical serum markers were analyzed using two-way repeated-measures Analysis of Variance (ANOVA) with Bonferroni correction for both within-groups and between group comparisons. A P-value of less than 0.05 was considered statistically significant. All P values were 2-sided and the statistical significant level was 0.05. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between April 2010 and August 2012, 77 patients were assessed for eligibility, of whom 70 were actually recruited and randomized to propofol group (N=35) or sevoflurane group (N=

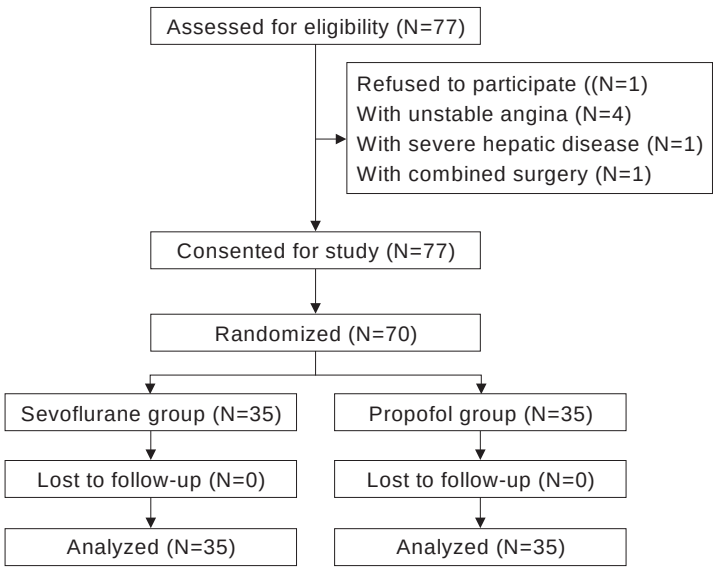

Figure 1. CONSORT Diagram Showing the Flow of Participants through Each Stage of the Randomized Trial.

Table 1. Preoperative and Intraoperative Characteristics.

	Sevoflurane group (N=35)	Propofol group (N=35)	P value
Age (years)	62 (7)	65 (8)	0.33
Weight (kg)	68 (65, 72)	61 (58, 68)	0.27
Sex, males	31 (89%)	33 (94%)	0.67
Smoking, N (%)			0.47
Current smokers	9 (26%)	6 (17%)	
Ex-smokers	15 (43%)	20 (57%)	
Never smoked	11 (31%)	9 (26%)	
Associated illness, N (%)			
Hypertension	26 (74%)	21 (60%)	0.32
Diabetes mellitus	12 (34%)	14 (40%)	0.80
Previous myocardial infarction	6 (17%)	10 (29%)	0.39
Glasgow Aneurysm score	64 (55, 72)	65 (54, 70)	0.88
Preoperative medications, N (%)			
β-blockers	17 (49%)	21 (60%)	0.47
Calcium channel antagonist	9 (26%)	7 (20%)	0.77
Statin	16 (46%)	18 (51%)	0.81
ACE inhibitor	11 (31%)	8 (23%)	0.59
Duration of anesthetic (minute)	287 (32)	269 (35)	0.64
Cross-Clamp time (minute)	60 (8)	55 (11)	0.23
Aneurysm diameter (mm)	73 (9)	68 (11)	0.59
Median operating time (min)	145 (21)	139 (19)	0.81

There were no statistically significant differences between groups on either variable listed. Continuous data were reported as means (SD) or median (25% percentile, 75% percentile). Categorical data were given as counts (percentages). ACE, angiotensin-converting enzyme.

35). The CONSORT diagram was summarized in figure 1. All patients completed the study with no patients lost to follow up. As table 1 showed, patients' baseline characteristics and operative characteristics, including preoperative medications, total operation time, aortic cross-clamping time, aneurysm diameter and Glasgow Aneurysm Score were similar in both groups (all $P>0.05$).

Intraoperative and postoperative data were summarized in table 2. Packed erythrocytes transfusion, intravenous fluid infusion and vasoconstrictors usage were comparable between groups during the operation and 24 hours after surgery (all $P>0.05$). The ventilator support time and ICU free days were both shorter in the propofol group compared with sevoflurane group (309 [215, 478] minutes vs. 440 [336, 620] minutes, $P=0.03$ and 2 [2, 4] days vs. 3 [2, 5] days, $P=0.04$, respectively), and the mean hospital free stay was 2 days shorter in the propofol group (10 vs. 12 days) but without statistical significance ($P=0.33$). All patients survived 30 days after operation. Major complications included new myocardial infarction (2 patients in each group), arrhythmia (3 patients in the propofol group and 2 patients in the sevoflurane group), and congestive cardiac failure (1 patient in the propofol group). None of the patients in two groups had cerebrovascular injury, renal damage requiring hemofiltration or MODS. Intraoperative hemodynamic data are shown in table 3.

Intestinal Injury

As shown in figure 2A, I-FABP levels increased significantly in both groups 30 minutes after cross-clamp release, and remained high until the first postoperative day. The sevoflurane group had a higher serum I- FABP concentration at 30 minutes, 4 hours after cross- clamp release than the propofol group (all $P<0.05$). Likewise, serum endotoxin levels and DAO activity progressively and significantly increased in both groups, returning to basal values 24 hours after surgery. In propofol group, endotoxin levels and DAO activity remained constant and were significantly lower than those in the sevoflurane group (all $P<0.01$).

In addition, no difference of the scores of intestinal injury severity was observed between groups at 72 hours after surgery ($P=0.53$, Table 2).

Evaluation of Systemic Inflammatory Response and Lipid Peroxidation

Serum markers of systemic inflammatory in-

Table 2. Intraoperative and Postoperative Data.

	Sevoflurane group (N=35)	Propofol group (N=35)	P value
Intraoperative			
Crystalloid (ml)	2,110 (2,000, 2,500)	2,230 (2000, 2,500)	0.55
Colloid (ml)	1,120 (500, 1500)	1,010 (500, 1,500)	0.69
Packed erythrocytes transfusion (ml)	370 (200, 500)	420 (300, 600)	0.23
FFP (ml)	210 (100, 200)	230 (200, 300)	0.81
Estimate blood loss (ml)	460 (216)	614 (342)	0.13
Urine output (ml)	550 (400, 830)	420 (300, 560)	0.16
Number of patients transfused	9 (26%)	4 (11%)	0.22
24 hours after operation			
Crystalloid (ml)	3,200 (3,000, 3,500)	3,416 (2,800, 3,500)	0.59
Colloid (ml)	400 (200, 500)	430 (300, 500)	0.64
Packed erythrocytes transfusion (ml)	200 (100, 300)	250 (200, 400)	0.74
FFP (ml)	100 (0, 200)	250 (0, 300)	0.12
Vasoconstrictors usage	2 (6%)	5 (14%)	0.43
Ventilator support time (minute)	440 (336, 620)	309 (215, 478)	0.03
ICU free days	3 (2, 5)	2 (2, 4)	0.04
Hospital free days	12 (7, 14)	10 (7, 12)	0.33
Intestinal injury grade			0.53
Normal	1 (3%)	3 (9%)	
Mild intestinal injury	24 (68%)	25 (71%)	
Moderate intestinal injury	9 (26%)	7 (20%)	
Severe intestinal injury	1 (3%)	0	
Myocardial infarction	2 (6%)	2 (6%)	1.0
Arrhythmia	2 (6%)	3 (9%)	0.64
Congestive cardiac failure	0	1 (3%)	0.41
Renal failure	0	0	
Neuralgic events	0	0	
MODS	0	0	
Death	0	0	

Continuous data were reported as means (SD) or median (25% percentile, 75% percentile). Categorical data were given as counts (percentages). FFP, fresh frozen plasma; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome.

Table 3. Intraoperative Hemodynamic Data.

	Group	Baseline	30 minutes after reperfusion	4 hours after reperfusion	8 hours after reperfusion	12 hours after reperfusion	24 hours after reperfusion
MAP (mm Hg)	Sevoflurane	84 (10)	71 (13)	72 (10)	72 (11)	84 (12)	80 (14)
	Propofol	87 (12)	76 (8)	74 (13)	75 (10)	82 (10)	85 (12)
HR (beats/minute)	Sevoflurane	67 (11)	84 (16)	82 (13)	80 (11)	82 (17)	83 (14)
	Propofol	64 (15)	77 (10)	76 (9)	79 (10)	84 (13)	82 (9)
CVP (cm H_2O)	Sevoflurane	8 (1)	10 (3)	9 (3)	9 (2)	10 (3)	9 (2)
	Propofol	7 (2)	9 (3)	8 (3)	8 (2)	9 (2)	8 (3)

All data were presented as means (SD). There were no statistically significant differences between the two groups at any time point. CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure.

creased postoperatively with both anesthetics from comparable baseline values. As shown in figure 2D, the IL-6 levels peaked 12 hours after the release of cross-clamp in both groups. However, the level in sevoflurane group was higher than that in propofol group (P=0.02). Different from the changes of IL-6 levels, TNF-α level gradually increased over the whole observational period and sharply peaked 24 hours after the release of the cross-clamp. Likewise, TNF-α level in sevoflurane group was higher than that in propofol group (P=0.04, Figure 2E).

As shown in figure 2F, the serum malondialdehyde levels in both groups increased transiently in

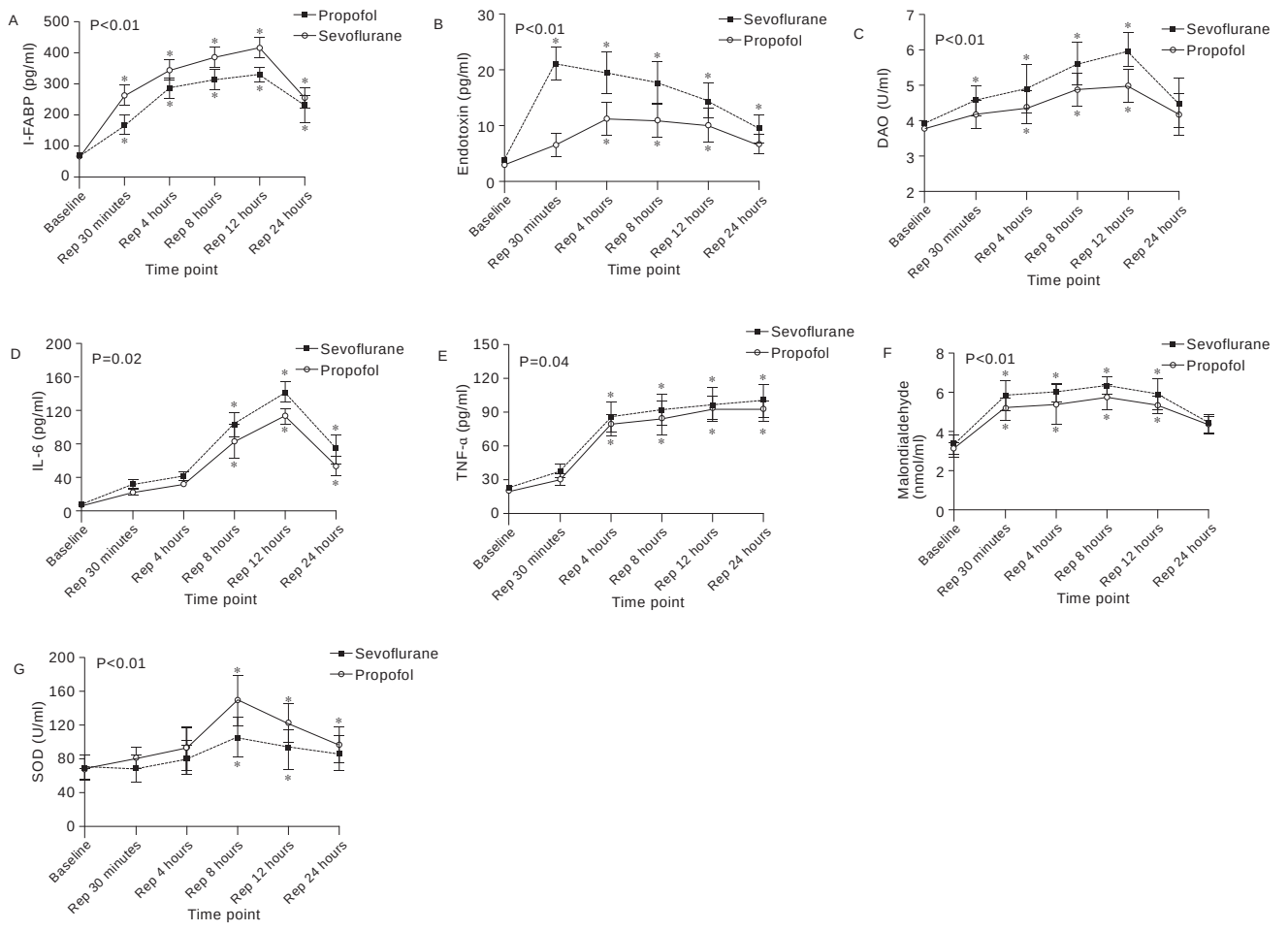

Figure 2. Biomarkers of Intestinal Injury as well as Variables Reflecting Oxidative Stress and Inflammatory Response at Various Time Points in Patients Undergoing Open Infrarenal AAA Repair (N=35 for Each Group).

A. Serum I-FABP concentration; B. Serum endotoxin level; C. Serum DAO activity; D. IL-6 concentration; E. TNF-α concentration; F. Serum malondialdehyde concentration; G. SOD activity. Data were represented as means (SD). *P<0.05 versus baseline; #P< 0.05 versus sevoflurane group.

AAA, abdominal aortic aneurysm; DAO, diamine oxidase; I-FABP, intestinal fatty acidbinding protein; IL-6, interleukin-6; Rep, reperfusion; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α.

the first 12 hours after the release of cross-clamp and returned to the baseline values 24 hours after reperfusion. Sevoflurane group demonstrated a significant increase in malondialdehyde level after reperfusion, whereas propofol significantly reduced the malondialdehyde levels in comparison to the sevoflurane group (P< 0.01).

Figure 2G showed that in the propofol group, SOD activity increased significantly 8 hours after cross-clamp release (68.8 ± 12.2 U/ml vs. 149.9 ± 30.6 U/ml, P<0.05). However, SOD activity in sevoflurane group remained constant after the release of cross-clamp, and the activity of SOD was significantly different between groups (P<0.01).

DISCUSSION

In this prospective, randomized, controlled trial, significant occurrence of intestinal injury in patients undergoing open infrarenal AAA repair was demonstrated by marked increases in the serum I-FABP and endotoxin levels and the serum DAO activity. Meanwhile, the results from this

investigation indicated that patients receiving propofol for elective open infrarenal AAA repair had less intestinal injury than patients receiving sevoflurane for the same intervention. This is inferred from significantly lower levels of the serum I-FABP, endotoxin and the DAO activity after cross-clamping release. Of note, the current data also showed that patients receiving propofol demonstrated a significantly shorter ventilator support time and ICU stay than those receiving sevoflurane. Nevertheless, the data presented herein were in good agreement with our recent studies in the laboratory which also reported intestinal protection by the application of propofol in rats undergoing superior mesenteric artery occlusion-induced intestinal I/R injury.

Previous studies have found that intestinal injury occurred following open AAA repair (21-23). The urine excretion ratio of lactulose and mannitol has previously been used to assess intestinal mucosal permeability of intestinal permeability in research, but it is not sensitive enough in critically ill patients (24). Different from the previous studies, three different markers which respectively reflect intestinal injury from different aspects, together with the intestinal dysfunction score were used in the present study to evaluate intestinal injury. I-FABP, being uniquely located at the tips of intestinal mucosal villi, is generally undetectable in the peripheral circulation, whereas it will increase rapidly when intestinal mucosal injury occurs. Therefore, I-FABP has been taken as a sensitive marker of early intestinal ischemia (17, 25). The serum endotoxin level was used to reflect the intestinal permeability in the present study. In addition, the marker for reflecting intestinal injury was serum DAO activity, which was also used as an index of small intestinal mucosal injury (26). In our study, the above three biomarkers increased significantly after the release of cross-clamp, which implied that the intestinal barrier function was disrupted after open AAA repair. Furthermore, our results showed that propofol, but not sevoflurane, could significantly alleviate those biomarkers reflecting intestinal injury, which to some extent indicated the improvement of intestinal barrier function.

The mechanism via which open infrarenal AAA repair induces intestinal injury has not been totally elucidated yet. It is postulated that intestine I/R could be one of the leading causes, which is accompanied with significant inflammatory cytokines release and ROS production during open abdominal surgery and conventional aneurysm repair (27, 28). This is strongly supported by our previous findings in a rat mode with superior mesenteric artery occlusion (29-31). Propofol has antioxidant and anti-inflammatory property which has been well documented in our previous studies (9, 10). The study by Yagmurdur et al. (32) showed that propofol could prevent burn injury induced increase in lipid peroxidation and attenuate gut mucosal epithelial apoptosis in rats. In addition, a recent study showed that propofol had the best antioxidant effect on oxidative stress in rats that underwent intestinal I/R procedure (33). In accordance with the previous reports, the present study also showed that open infrarenal AAA repair caused significant increases in serum malondialdehyde levels as well as reduction in SOD activity, further suggesting that lipid preoxidation and inflammatory response might be one of the causes for intestinal injury during open AAA repair. Furthermore, our results showed that protective effects of propofol against intestinal injury were also markedly higher compared with sevoflurane, which could be attributable to its suppression of the releases of ROS.

Inflammatory responses in the intestine were involved in the pathogenesis of gastrointestinal dysfunction. Cytokines and inflammatory mediators such as TNF-α and IL-6 could induce damages of microvilli, tight junction between enterocytes and paracellular junction, which would lead to increased intestinal permeability (34). In this study, propofol had better inhibitory effects on the releases of IL-6 and TNF-α, indicating that propofol has more protective effect on intestinal injury by inhibiting the proinflammatory mediators than sevoflurane.

As a commonly used halogenated volatile anesthetic, sevoflurane was documented to induce better organ protection than propofol (16, 35-37). But to our knowledge, the impact of commonly applied anesthetics such as sevoflurane and propofol on the intestinal I/R has not been measured in patients undergoing open AAA repair. In contrast, the findings herein showed

that patients receiving propofol for elective open AAA repair had less intestinal injury than patients receiving sevoflurane. That might be attributable to different clinical settings in which propofol and sevoflurane could have different performances. In addition, the pathogenesis between organs could exist due to different pathophysiological process.

Several potential limitations existed in the present study. Firstly, both propofol and sevoflurane were used as a part of a multidrug anesthetic regimen. All patients received a continuous infusion of remifentanil throughout the operation. We cannot exclude the effect of remifentanil on intestinal injury, even if no studies previously showed its intestinal protective effect. Secondly, despite the power analysis to calculate the sample size, the effective group size was much smaller duo to detect a significant difference in the scores of intestinal injury severity adverse between groups. Thirdly, propofol conferring better intestinal protection than sevoflurane could be related to the dosage of propofol or the concentration of sevoflurane we chose in this study. Further studies will need to evaluate the question of a dose dependency of intestinal protective effects.

In conclusion, patients receiving propofol for elective open infrarenal AAA repair had significantly lower levels of biomarker reflecting intestinal injury than patients receiving sevoflurane for the same procedure. This study supported intestinal protective effects of propofol so far only documented in the laboratory and suggested that the choice of an anesthetic with respect to intestinal reperfusion injury might be of importance in the surgical patient population. The underlying mechanisms and the clinical implications of these beneficial effects remain subject to further investigation.

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The authors declare no other competing interests.

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References

1. Mallick IH, Yang W, Winslet MC, Seifalian AM. Ischemia- reperfusion injury of the intestine and protective strategies against injury. Dig Dis Sci 2004; 49: 1359-77.
2. Deitch EA. Role of the gut in multiple system organ failure. Curr Opin Crit Care 2001; 7: 92-8.
3. Mitsuoka H, Kistler EB, Schmid- Schonbein GW. Protease inhibition in the intestinal lumen: attenuation of systemic inflammation and early indicators of multiple organ failure in shock. Shock 2002; 17: 205-9.
4. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. The antioxidant potential of propofol (2, 6-diisopropylphenol). Br J Anaesth 1992; 68: 613-8.
5. Thiry JC, Hans P, Deby-Dupont G, Mouythis-Mickalad A, Bonhomme V, Lamy M. Propofol scavenges reactive oxygen species and inhibits the protein nitration induced by activated polymorphonuclear neutrophils. Eur J Pharmacol 2004; 499: 29-33.
6. Xia Z, Huang Z, Ansley DM. Large-dose propofol during cardiopulmonary bypass decreases biochemical markers of myocardial injury in coronary surgery patients: a comparison with isoflurane. Anesth Analg 2006; 103: 527-32.
7. De Hert SG, Cromheecke S, ten Broecke PW, Mertens E, De Blier IG, Stockman BA, et al. Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high- risk patients. Anesthesiology 2003; 99: 314-23.
8. Bovill JG. Intravenous anesthesia for the patient with left ventricular dysfunction. Semin Cardiothorac Vasc Anesth 2006; 10: 43-8.
9. Liu KX, Rinne T, He W, Wang F, Xia Z. Propofol pretreatment attenuates intestinal mucosa injury induced by intestinal ischemia- reperfusion in the rats. Can J Anaesth 2007; 54: 366-74.
10. Liu KX, Chen SQ, Huang WQ, Li YS, Irwin MG, Xia Z. Propofol pretreatment reduces ceramide production and attenuates intestinal mucosal apoptosis induced by intestinal ischemia/reperfusion in rats. Anesth Analg 2008; 107: 1884-91.
11. Schlosser FJ, Vaartjes I, van der Heijden GJ, Moll FL, Verhagen HJ, Muhs BE, et al. Mortality after elective abdominal aortic aneurysm repair. Ann Surg 2010; 251: 158-64.
12. Bown MJ, Nicholson ML, Bell PR, Sayers RD. Cytokines and inflammatory pathways in the pathogenesis of multiple organ failure following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2001; 22: 485-95.
13. Willoughby L, Dark P, Warhurst G. Investigation of systemic and mesenteric inflammatory signaling and gut-derived endothelial toxicity in patients undergoing high- risk abdominal aortic surgery. Shock 2011; 36: 121-7.
14. Khaira HS, Maxwell SR, Thomason H, Thorpe GH, Green MA, Shearman CP. Antioxidant depletion during aortic aneurysm repair. Br J Surg 1996; 83: 401-3.
15. Ballester M, Llorens J, Garcia-de-la-Asuncion, Perez-Griera J, Tebar E, Martinez-Leon J, et al. Myocardial oxidative stress protection by sevoflurane vs. propofol: a randomized controlled study in patients undergoing off- pump coronary artery bypass graft surgery. Eur J Anaesthesiol 2011; 28: 874-81.
16. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology 2003; 99: 826-33.
17. Kanda T, Fujii H, Tani T, Murakami H, Suda T, Sakai Y, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology 1996; 110: 339-43.
18. Reintam A, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal failure score in critically ill patients: a prospective observational study. Crit Care 2008; 12: R90.
19. Biancari F, Leo E, Ylönen K, Vaarala MH, Rainio P, Juvonen T. Value of the Glasgow Aneurysm Score in predicting the immediate and long- term outcome after elective open repair of infrarenal abdominal aortic aneurysm. Br J Surg 2003; 90: 838-44.
20. Lerman J. Study design in clinical research: sample size estimation and power analysis. Can J Anaesth 1996; 43: 184-91.
21. Roumen RM, Van der Vliet A, Wevers RA, Goris RJ. Intestinal permeability is increased after major vascular surgery. J Vasc Surg 1993; 17: 734-7.
22. Neary P, Hurson C, Briain DO, Brabazon A, Mehigan D, Keaveny TV, et al. Abdominal aortic aneurysm repair and colonic infarction: a risk factor appraisal. Colorectal Dis 2007; 9: 166-72.
23. Perry RJ, Martin MJ, Eckert MJ, Sohn VY, Steele SR. Colonic ischemia complicating open vs endovascular abdominal aortic aneurysm repair. J Vasc Surg 2008; 48: 272-7.
24. Rupani B, Caputo FJ, Watkins AC, Vega D, Magnotti LJ, Lu Q, et al. Relationship between disruption of the unstirred mucus layer and intestinal restitution in loss of gut barrier function after trauma hemorrhagic shock. Surgery 2007; 141: 481-9.
25. Pelsers MM, Hermens WT, Glatz JF. Fatty acid binding proteins as plasma markers of tissue injury. Clin Chim Acta 2005; 352: 15-35.
26. Bragg LE, Thompson JS, West WW. Intestinal diamine oxidase levels reflect ischemic injury. J Surg Res 1991; 50: 228-33.
27. Thompson MM, Nasim A, Sayers RD, Thompson J, Smith G, Lunec J, et al. Oxygen free radical and cytokine generation during endovascular and conventional aneurysm repair. Eur J Vasc Endovasc Surg 1996; 12: 70-85.
28. Tsuchiya M, Sato EF, Inoue M, Asada A. Open abdominal surgery increase intraoperative oxidative stress: can it be prevented? Anesth Analg 2008; 107:

1946-52.
29. Liu KX, Li YS, Huang WQ, Chen SQ, Wang ZX, Liu JX, et al. Immediate postconditioning during reperfusion attenuates intestinal injury. Intensive Care Med 2009; 35: 933-42.
30. Liu KX, Wu WK, He W, Liu CL. Ginkgo biloba extract (EGb 761) attenuates lung injury induced by intestinal ischemia/reperfusion in rats: Roles of oxidative stress and nitric oxide. World J Gastroenterol 2007; 13: 299-305.
31. Liu KX, Li YS, Huang WQ, Li C, Liu JX, Li Y. Immediate but not delayed postconditioning during reperfusion attenuates acute lung injury induced by intestinal ischemia/reperfusion in rats: comparison with ischemic preconditioning. J Surg Res 2009; 157: e55-62.
32. Yagmurdur H, Aksoy M, Arslan M, Baltaci B. The effects of propofol and ketamine on gut mucosal epithelial apoptosis in rats after burn injury. Eur J Anaesthesiol 2007; 24: 46-52.
33. Azeredo MA, Azeredo LA, Eleuthério EC, Schanaider A. Propofol and N-Acetylcysteine attenuate oxidative stress induced by intestinal ischemia/reperfusion in rats. protein carbonyl detection by immunoblotting. Acta Cir Bras 2008; 23: 425-8.
34. Gong JP, Wu CX, Liu CA, Li SW, Shi YJ, Yang K, et al. Intestinal damage mediated by Kupffer cells in rats with endotoxemia. World J Gastroenterol 2002; 8: 923-7.
35. Bedirli N, Ofluoglu E, Kerem M, Utebey G, Alper M, Yilmazer D, et al. Hepatic energy metabolism and the differential protective effects of sevoflurane and isoflurane anesthesia in a rat hepatic ischemia-reperfusion injury model. Anesth Analg 2008; 106: 830-7.
36. Tiefenthaler W, Pehboeck D, Hammerle E, Kavakebi P, Benzer A. Lung function after total intravenous anaesthesia or balanced anaesthesia with sevoflurane. Br J Anaesth 2011; 106: 272-6.
37. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger KU, et al. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. Br J Anaesth 2011; 106: 840-50.