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see commentary on page 240

Anesthetics influence the incidence of acute kidney injury following valvular heart surgery

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Propofol has been shown to provide protection against renal ischemia/reperfusion injury experimentally, but clinical evidence is lacking. Here we studied the effect of propofol anesthesia on the occurrence of acute kidney injury following heart surgery with cardiopulmonary bypass. One hundred and twelve patients who underwent valvular heart surgery were randomized to receive either propofol or sevoflurane anesthesia, both with sufentanil. Using Acute Kidney Injury Network criteria, significantly fewer patients developed acute kidney injury postoperatively in the propofol group compared with the sevoflurane group (6 compared with 21 patients). The incidence of severe renal dysfunction was significantly higher in the sevoflurane group compared with the propofol group (5 compared with none). The postoperative cystatin C was significantly lower in the propofol group at 24 and 48 h. Serum interleukin-6 at 6 h after aorta cross-clamp removal, C-reactive protein at postoperative day 1, and segmented neutrophil counts at postoperative day 3 were also significantly lower in the propofol group. Thus, propofol anesthesia significantly reduced the incidence and severity of acute kidney injury in patients undergoing valvular heart surgery with cardiopulmonary bypass compared with sevoflurane. This beneficial effect of propofol may be related to its ability to attenuate the perioperative increase in proinflammatory mediators.

Kidney International (2014) **86,** 414–422; doi:10.1038/ki.2013.532; published online 15 January 2014

KEYWORDS: acute kidney injury; cardiac surgery; cardiopulmonary bypass; inflammation; ischemia–reperfusion; propofol

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Received 14 May 2013; revised 24 October 2013; accepted 31 October 2013; published online 15 January 2014

Acute kidney injury (AKI) following cardiac surgery, even when mild and transient, undoubtedly poses the patients to increased risk of prolonged intensive care unit (ICU) stay, morbidity, and mortality.[1,2] Yet, its prevention proves to be difficult as the reported incidence of AKI reaches up to 40% depending on the type of surgery and the adopted definition of it.[1–3] The underlying mechanisms involved in the pathogenesis of AKI after cardiac surgery are multifactorial and are not completely understood, currently. Still, apart from the patient-related factors, cardiopulmonary bypass (CPB), which inevitably causes oxidative stress, ischemia–reperfusion (I/R) injury, and systemic inflammatory response, has been constantly incriminated as a major factor in causing AKI.[4,5] Even in the absence of a surgery-related overt ischemic insult by vascular clamps, CPB invariably causes injury to the renal medulla as it is prone to ischemic damage for having a unique blood supply with a limited oxygen reserve.[4]

Propofol is a widely used intravenous anesthetic agent, which bears structural similarity with the endogenous antioxidant α-tocoferol.[6] Propofol also has been shown to possess anti-inflammatory and immune-modulatory properties.[7,8] While volatile anesthetics have been well known to exert organ-protective effect against I/R injury experimentally, several animal studies suggested that propofol was more effective in attenuating the development of AKI after exposure to anoxic circumstances when compared with the volatile anesthetic agents.[7,8]

Considering the putative mechanisms leading to AKI, the antioxidant and anti-inflammatory properties of propofol may theoretically be able to attenuate renal injury in patients undergoing cardiac surgery with CPB. Although cumulative evidence suggests the lack of renoprotective effect by volatile anesthetics in cardiac surgical patients despite their solid experimental background,[9,10] a trial validating the efficacy of propofol as an anesthetic agent on preventing AKI after cardiac surgery would be worth noting.

The aim of this prospective, randomized, and controlled trial was to investigate the effect of propofol anesthesia on renal protection in patients undergoing CPB for valvular heart surgery, which comprises a high risk for AKI.

RESULTS

Valvular heart surgery was performed as planned in all patients, and complete follow-up data until discharge from the 112 patients were analyzed without any missing data. No relevant clinical problem occurred with either of the two anesthetic methods. Patients' demographics, preoperative characteristics including Cleveland Clinic score and EuroSCORE, and surgeries performed were similar between two groups (Table 1).

Operative data including durations of anesthesia, aortic cross-clamp (ACC) and CPB, fluid balance including the amounts of ultrafiltration, and packed erythrocyte transfusion requirement were similar between the two groups. The amount of norepinephrine required during the operation was significantly greater in the sevoflurane group (Table 2). In the propofol group, the infusion rates of propofol were 106 ± 36 and 125 ± 38 μg/kg/min during CPB and the entire operation period, respectively. Intraoperative hemodynamic variables including cardiac index were comparable between the groups (Table 3).

The total amount of infused fluid, blood loss, and urine output until 72 h after the operation was comparable between the groups. However, furosemide requirements during the first 24 h ($P = 0.035$) and 48–72 h ($P = 0.029$) after the operation were significantly higher in the sevoflurane group compared with the propofol group (Table 4).

Postoperatively, AKI occurred in 21 patients (37.5%) of the sevoflurane group compared with only 6 patients (10.7%) of the propofol group ($P = 0.001$). The number of patients with urine output of <0.5 ml/kg per hour continuously over 6 h but within 48 h after the operation was 9 (16.1%) in the sevoflurane group and 2 (3.6%) in the propofol group, respectively ($P = 0.026$). Five (8.9%) patients were diagnosed with AKI classified as Acute Kidney Injury Network stage 2 or 3 and two of these patients received dialysis in the sevoflurane group, while none in the propofol group ($P = 0.022$). The interaction of group and time in the creatinine, cystatin C, and creatine kinase-MB (CK-MB) levels ($P = 0.027$, 0.009, and 0.031, respectively) were significant between the groups in the linear mixed-model analysis. *Post hoc* analysis with Bonferonni correction revealed that cystatin C levels at 24 and 48 h postoperatively and creatine kinase-MB (CK-MB) levels at 48 h postoperatively were significantly lower in the propofol group compared with the sevoflurane group. The number of patients in whom estimated glomerular filtration rate (eGFR) declined $>30\%$ from the baseline value was significantly greater in the sevoflurane group compared with the propofol group (18 (32.1%) vs. 5 (8.9%), $P = 0.002$). The number of patients showing an increase in cystatin C levels $>25\%$ from the baseline value was greater in the sevoflurane group than in the propofol group (22 (39.3%) vs. 11 (19.6%), $P = 0.023$) (Table 5).

The interaction of group and time in serum interleukin (IL)-6, C-reactive protein (CRP) levels, and segmented neutrophil counts ($P = 0.019$, 0.027, and 0.007, respectively) were significant between the groups in the linear mixed-model analysis. After *post hoc* analysis with Bonferonni correction, serum levels of IL-6 were significantly lower in the propofol group at 6 h after declamping of ACC, and serum concentration of CRP at postoperative day (POD) 1 and segmented neutrophil counts at POD 3 were significantly lower in the propofol group compared with the sevoflurane group (Figure 1).

The length of hospital stay was significantly shorter in the propofol group compared with the sevoflurane group, whereas other postoperative outcomes including duration of ventilator care, ICU stay, and in-hospital mortality were similar between the groups (Table 6).

None of the patients developed unexplained lactic acidosis, rhabdomyolysis, or dyslipidemia, indicating propofol infusion syndrome.

Table 1 | Patient demographics and preoperative clinical data

Variables	Sevoflurane ($n = 56$)	Propofol ($n = 56$)
Age (years)	58.8 ± 12.3	58.1 ± 12.2
Female gender	32 (57.1)	29 (51.8)
Body mass index (kg/m^2)	23.3 ± 3.3	24.1 ± 3.7
Operation		
Aortic valve replacement	18 (32.1)	18 (32.1)
Mitral valve replacement only	28 (50)	24 (42.9)
Mitral valve replacement with TAP	6 (10.7)	6 (10.7)
Double valve replacement	2 (3.6)	5 (8.9)
Bental	1 (1.8)	2 (3.6)
Redo	1 (1.8)	1 (1.8)
Diabetes mellitus	7 (12.5)	9 (16.1)
Hypertension	16 (28.6)	18 (32.1)
Cerebrovascular accidents	7 (12.7)	4 (7.1)
Congestive heart failure	5 (8.9)	4 (7.1)
Chronic obstructive pulmonary disease	2 (3.6)	1 (1.8)
NYHA classification		
I	24 (42.9)	27 (48.2)
II	28 (50)	27 (48.2)
III	4 (7.1)	2 (3.6)
Preoperative ejection fraction	63.1 ± 10.1	65.2 ± 11.3
Medications		
β-Blockers	20 (35.7)	16 (28.6)
Calcium channel blockers	14 (25)	11 (19.6)
Renin–angiotensin system antagonist	20 (35.7)	21 (37.5)
Diuretics	36 (64.3)	35 (62.5)
EuroSCORE	2.9 ± 1.7	3.2 ± 2.3
Cleveland Clinic score	1.8 ± 0.8	1.9 ± 0.7

Abbreviations: NYHA, New York Heart Association; TAP, tricuspid annuloplasty.
Values are mean ± s.d. or number of patients (%).

DISCUSSION

In spite of advances in CPB technology, the incidence of AKI after cardiac surgery has increased during the past decade.[11] The pathogenesis of AKI after cardiac surgery encompasses complex interplays among multiple factors, CPB-related I/R injury, oxidative stress, and activation of systemic inflammatory reaction have been regarded as major determinants.[4,5] Numerous strategies including pharmacologic and