Comparative study between the effect of propofol and sevoflurane on renal reperfusion injury after suprarenal infracoeliac aortic surgery

Tamer Attia Abdelmalek[a], Mohamed Hany Kamal[b], Nashwa Sami Elzayyat[c], Dalia Ibrahim Ramadan[d]

[a]Assistant Lecturer of Anesthesia, Teodor Belharz Institute, [b]Professor of Anesthesia, [c]Assistant Professor of Anesthesia, [d]Assistant Professor of Clinical Pathology, Cairo University, Cairo, Egypt

Correspodence to Nashwa Sami Elzayyat, MD, Assistant Professor of Anesthesia, Cairo University, 12 Ahmed Mokhtar Hegazy, Manial, Cairo, Egypt
Tel: 01222394934;
e-mail: nanosami@yahoo.com

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Introduction
This study was designed to assess and compare the effect of propofol total intravenous anesthesia as against sevoflurane volatile induction and maintenance of anesthesia during suprarenal aortic clamping as part of renal protection strategies utilizing serum creatinine and proinflammatory cytokines: tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) as stress biomarkers.
Patients and methods
A total of 30 patients scheduled for major elective abdominal suprarenal infracoeliac aortic surgery were included. Fifteen of them received propofol total intravenous anesthesia (group P) and the other 15 received sevoflurane volatile induction and maintenance of anesthesia (group S). Serum creatinine level and plasma TNF-α and IL-1β were measured at the following intervals: before the initiation of surgery (T0), 15 min after reperfusion (T1), and 24 h (T2), 48 h (T3), and 72 h (T4) after end of surgery.
Results
Group S demonstrated higher levels of serum creatinine, plasma TNF-α, and IL1-β following the release of cross-clamp than group P. The highest level of serum creatinine was observed at T2 and then values tended to decline afterward in both groups ($P < 0.001$), whereas a significant increase over time for both plasma TNF-α and IL-1β was observed in the two studied groups ($P < 0.001$); the highest levels were detected at T4.
Conclusion
In this surgical setting, propofol is superior to sevoflurane in reducing renal ischemia and oxidative stress as reflected by lower values of serum creatinine and plasma proinflammatory cytokines: TNF-α and IL-1β.

Keywords:
propofol, renal ischemia–reperfusion injury, sevoflurane

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Introduction

Interest has been focused on the potential of anesthetics to protect against oxidant-mediated cell damage [1]. This is obvious in certain surgical settings where ischemia–reperfusion (I/R) injury occurs as in organ transplantation as well as in patients with compromised liver, kidney, or heart [2].

Aortic clamping causes an I/R syndrome that affects all organs and tissues at different levels. The existence of the systemic inflammatory syndrome means that the sequels are not only local, but also may affect several other distant organs, causing dysfunction and multiorgan failure [3]. Findings show that renal ischemia after suprarenal aortic clamping induces severe kidney damage, characterized by an increase in creatinine and proinflammatory cytokine levels — for example, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) [4,5].

Moreover, exposure to volatile anesthetics was accused for increasing the susceptibility of cells to oxidant damage [6], the exact mechanism of which remains to be elucidated; however, it was suggested that they may serve as substrates for the production of their own free radicals [7]. In contrast, few studies showed an antioxidant property of sevoflurane as it has the smallest changes in expression of proinflammatory cytokines among all other inhalation anesthetics [8]. A cardioprotective effect against reperfusion injury has been attributed to its free radical scavenging properties and to the reduction of postischemic adhesion of neutrophils [9,10].

Intravenous anesthetic 2,6-di-isopropylphenol (propofol) has also been shown to have antioxidant properties [11]. Several mechanisms of action have been proposed including interference with lipid peroxidation [12], acting on cellular enzymatic system [13], and reduction of neutrophil migration

with subsequent action as a scavenger of peroxynitrites free radical [14].

The aim of this study was to investigate the effect of propofol total intravenous anesthesia (TIVA) in renal protection from I/R injury during suprarenal infracoeliac aortic surgery with Dacron tube grafting, in comparison with sevoflurane volatile induction and maintenance of anesthesia (VIMA).

Patients and methods

Patient population

This prospective pilot study was approved by the institutional ethical committee. Written informed consent was obtained from all patients. From January 2011 to March 2012, 30 adult patients were scheduled to undergo elective abdominal suprarenal infracoeliac aortic surgery at the General Surgery Department, Kasr Al-Aini Hospital.

Exclusion criteria were: children below 18 years, ASA more than III, poor ventricular functions by preoperative echocardiography (EF < 40%), poor pulmonary functions, renal insufficiency (creatinine>1.5 mg/dl), hepatic impairment (ALT or AST>150 U/l), any coagulopathies, sensitivity to any of the studied drugs, and malignancies.

Study groups

Patients were randomly allocated into two groups using opaque sealed envelopes. Anesthesiologist was blinded to group allocation.

Group P (n = 15): received propofol TIVA.

Group S (n = 15): received sevoflurane VIMA.

Premedication

All patients received standard premedication in the form of 10 mg oral diazepam the night before surgery and after arriving the preoperative area; intravenous midazolam was administered at a dose of 0.05 mg/kg.

Perioperative procedure

In the operating room, all patients were monitored by five-lead ECG, radial artery cannula, pulse oximetry, capnography, urinary catheter, central venous pressure line, and temperature monitoring.

Spinal cord protection

It was achieved by placement of a lumbar cerebrospinal fluid drain in the awake patient that intermittently drained the cerebrospinal fluid in predefined aliquots (typically 10–15 ml) over the whole operating time.

Induction and maintenance

According to randomization, patients were divided into the following groups:

Group P (n = 15): they received propofol 2–2.5 mg/kg, lidocaine 1.5 mg/kg, and fentanyl 1–2 μg/kg followed by continuous intravenous infusion of propofol (TIVA) using syringe pump at 6 mg/kg/h until the end of surgery.

Group S (n = 15): they received sevoflurane VIMA. Patients were instructed to breathe out the residual volume, after which a clear plastic face mask was tightly fitted. Patients took a vital capacity breath of sevoflurane 8% in oxygen 100% (40 l/min), which they held as long as possible and they had to be assured and instructed about the presence of a 'sweet smell'. When they could not held their breath anymore, they were allowed to breathe normally. After loss of consciousness (absence of lash reflex), sevoflurane concentration was reduced to 3% and assisted ventilation was started with a face mask. Assisted ventilation was then switched gradually to standard controlled ventilation with sevoflurane 2%, and tracheal intubation was performed.

Atracurium intravenous (0.5 mg/kg) was injected to facilitate tracheal intubation in all patients in both groups. General anesthesia was maintained in both groups with intermittent positive pressure ventilation (IPPV) delivering minute volume (70–80 ml/kg) to maintain a PCO_2 at 32–35 mmHg.

In both groups, fentanyl infusion at 1 μg/kg/h was given throughout the whole operating time. Intraoperative relaxation was maintained by atracurium (0.4 mg/kg/h) and air : oxygen = 3 : 1 (FiO_2 = 40%).

By the end of surgery and after establishment of stable hemodynamics, temperature, and hemostasis, reversal of muscle relaxation was achieved by neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. Any hypertension or tachycardia was treated by esmolol (0.2–0.5 mg/kg) and nitroglycerine. Patients were extubated and transferred to the postoperative ICU. Postoperative analgesia was achieved using patient controlled analgesia.

Samples

Five consequent (5 ml each) venous blood samples were taken from each patient at the following intervals: before the initiation of surgery (T0), 15 min after reperfusion (release of cross-clamp) (T1), and 24 h (T2), 48 h (T3), and 72 h (T4) after end of surgery for measurement of serum creatinine level and plasma TNF-α and IL-1β. Samples were centrifuged at ~1000g; plasma was removed, aliquoted, and stored at -20°C until the time of the assay. All assays were performed by an investigator blinded to the study group assignment.

Creatinine assay was performed on Hitachi analyzer 917 (Roche Diagnostics GmbH, Mannheim, Germany) by kinetic colorimetric assay.

TNF-α and IL-1β were estimated by the quantitative sandwich enzyme immunoassay technique (Cat #DTA00C and DLB50, respectively; R&D Systems Inc., Minneapolis, Minnesota, USA).

Statistical analysis

Quantitative data were presented as mean ± SD, whereas qualitative data were presented as number (%). Differences between groups were detected using Student's *t*-test, whereas differences within groups were detected using repeated measure analysis of variance and/or Friedman/Wilcoxon ranks tests as appropriate. Qualitative data were compared by the χ^2-test. Statistical analysis was carried out on SPSS (version 17.0; SPSS Inc., Chicago, Illinois, USA) for Windows. *P* values less than 0.05 were considered statistically significant.

Results

This study was conducted on 30 patients scheduled for major elective abdominal suprarenal infracoeliac aortic surgery. Table 1 summarizes demographic data and baseline information of the two groups.

Serum creatinine and plasma proinflammatory cytokines level

Serum creatinine and creatinine percentage change were significantly higher in group S compared with group P at all intervals following the release of cross-clamp ($P < 0.001$). In both groups, the highest levels were observed at T2 (creatinine: 6.42 ± 0.38 and 4.34 ± 0.18, creatinine percentage change: 481 ± 102.6 and 287 ± 57.4 in groups S and P, respectively), then values tended to decline afterward in both groups ($P < 0.001$).

Regarding plasma TNF-α and percentage change, significantly higher levels were seen in group S as compared with group P at T2, T3, and T4 ($P < 0.001$). As for plasma IL-1β, a significant difference between the two groups was detected at all times following the release of cross-clamp, being higher in group S ($P = 0.022$ at T1 and $P < 0.001$ at the rest); however, IL-1β percentage change demonstrated such difference at T2, T3, and T4 ($P < 0.001$).

A significant increase over time for both plasma TNF-α and IL-1β and their percentage changes was observed in the two studied groups ($P < 0.001$); highest levels were detected at T4 (TNF-α: 409.87 ± 12.98 and 263.67 ± 11.4, TNF-α percentage change: 2067.2 ± 119.9 and 1297.6 ± 81.1; IL-1β: 415.95 ± 9.46 and 279.86 ± 10.83, IL-1β percentage change: 811.8 ± 107.5 and 496.1 ± 59.8 in groups S and P, respectively) (Tables 2 and 3).

Discussion

In the current study, serum creatinine was measured as an indicator of renal ischemia and TNF-α and IL-1β as indicators of systemic inflammatory response. Levels of serum creatinine and plasma TNF-α and IL-1β were higher in group S at most intervals. A significant increase in plasma TNF-α and IL-1β levels was observed throughout time in both groups; however, the highest serum creatinine level was seen 24 h after the release of cross-clamp then tended to decline.

Renal injury accounts for 10–18% of causes of early mortality after aortic aneurysm surgery [15]. The suprarenal aortic clamping and unclamping results in adherence of polymorphonuclear leukocytes to the vascular intima under the effect of P-selectin elevation,

Table 1 Demographic and clinical data of the two studied groups

	Propofol (*n* = 15)	Sevoflurane (*n* = 15)	*P*
Age (years)	62 ± 5.68	64.86 ± 6.9	0.322
Weight (kg)	83.5 ± 11.3	82 ± 7.75	0.682
Cross-clamping time (min)	67.46 ± 9.2	69.26 ± 7.2	0.589
HR (beats/min)	82.9 ± 8.2	83.7 ± 6.1	0.763
MABP (mmHg)	67.5 ± 9.3	69.3 ± 8.7	0.589
ASA II : III	7 : 8	10 : 5	0.269
Male : female	10 : 5	8 : 7	0.456

Data presented as mean ± SD and as numbers; ASA, American Society of Anesthesiologists; HR, heart rate; MABP, mean arterial blood pressure.

Table 2 Concentrations of the three studied parameters throughout the time in the two studied groups

	Propofol (*n* = 15)	Sevoflurane (*n* = 15)	*P**
Creatinine			
T0	1.14 ± 0.14[a]	1.12 ± 0.14[a]	0.799
T1	3.66 ± 0.2[b]	4.46 ± 0.25[b]	<0.001
T2	4.34 ± 0.18[c]	6.42 ± 0.38[c]	<0.001
T3	3.37 ± 0.31[b]	6.14 ± 0.44[c]	<0.001
T4	2.46 ± 0.3[d]	5.06 ± 0.48[d]	<0.001
P†	<0.001	<0.001	
TNF-α			
T0	18.91 ± 1.2[a]	18.94 ± 0.82[a]	0.931
T1	116.7 ± 3.8[b]	116.56 ± 2.5[b]	0.913
T2	206.5 ± 3.7[c]	364.99 ± 10.23[c]	<0.001
T3	250.41 ± 8.9[d]	381.45 ± 9.9[c]	<0.001
T4	263.67 ± 11.4[d]	409.87 ± 12.98[d]	<0.001
P†	<0.001	<0.001	
IL-1β			
T0	47.35 ± 4.65[a]	46.12 ± 4.6[a]	0.472
T1	115.84 ± 4.6[b]	121.27 ± 7.18[b]	0.022
T2	203.08 ± 6.6[c]	362.88 ± 18.76[c]	<0.001
T3	213.72 ± 27.55[c]	393.21 ± 16.7[c]	<0.001
T4	279.86 ± 10.83[d]	415.95 ± 9.46[d]	<0.001
P†	<0.001	<0.001	

Data presented as mean ± SD; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; Groups bearing the same initials are not statistically significant at $P < 0.05$; **P* difference between the two groups; †*P* within time difference in the same group.

Table 3 Percentage change of the three studied parameters at the specified time intervals compared with the basal levels in the two studied groups

	Propofol (n = 15)	Sevoflurane (n = 15)	P^*
Creatinine			
T1	225.7 ± 40.2[a]	302.8 ± 63.2[a]	<0.001
T2	287 ± 57.4[b]	481 ± 102.6[b]	<0.001
T3	201.2 ± 52.8[a]	454.2 ± 87.1[b]	<0.001
T4	118.8 ± 37.4[c]	357.3 ± 72.9[c]	<0.001
$P^\dagger$	<0.001	<0.001	
TNF-α			
T1	519.6 ± 49.3[a]	516.2 ± 28.5[a]	0.820
T2	996.3 ± 1829.5[b]	1829.6 ± 95[b]	<0.001
T3	1228.4 ± 87.1[c]	1916.6 ± 96.4[c]	<0.001
T4	1297.6 ± 81.1[d]	2067.2 ± 119.9[d]	<0.001
$P^\dagger$	<0.001	<0.001	
IL-1β			
T1	147.2 ± 29.9[a]	165.6 ± 32.6[a]	0.118
T2	332.5 ± 41.6[b]	692.5 ± 70.8[b]	<0.001
T3	356.2 ± 77.9[b]	759.8 ± 86.3[c]	<0.001
T4	496.1 ± 59.8[c]	811.8 ± 107.5[d]	<0.001
$P^\dagger$	<0.001	<0.001	

Data presented as mean ± SD; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; Groups bearing the same initials are not statistically significant at P<0.05; $^*P$ difference between the two groups; $^\dagger P$ within time difference in the same group.

which is rapidly translocated to the endothelial cell surfaces within 5 min of revascularization of the organ [16]. Local production of proinflammatory cytokines, IL-1β and/or TNF-α, by these leukocytes, in turn, induces P-selectin and E-selectin expression on endothelium, which continues a cascade of events that increase cell adherence and infiltration of the injured tissues [17,18].

Influence of propofol on the oxidative system has gained a lot of interest, and the literature on propofol is rather abundant. In contrast, the literature on sevoflurane and stress response modulation is few. Moreover, studies comparing the effects of propofol and sevoflurane in aortic aneurysm surgeries are rare, even rarer when it comes to studies on humans.

Among the very few studies using both drugs in an experimental model of aortic reconstructive surgery working on piglets, authors were able to demonstrate similar results, whereby group P was associated with lower concentrations of plasma creatinine, myeloperoxidase, TNF-α, IL-1β, interferon-γ, superoxide anion (SOA), superoxide dismutase, malondialdehyde, and inducible nitric oxide synthase (iNOS) in comparison with group S, indicating more pronounced protective potentials of propofol on reducing renal I/R injury in these surgical settings [4,5]. These data are in good agreement with studies reporting the potential benefit of propofol as an antioxidant in different in-vivo and in-vitro models, in situations of I/R leading to systemic inflammatory syndrome [19,20].

Attempts to link the propofol molecule and the observed antioxidant effect have been developed in different studies. According to these studies, propofol would inhibit or at least decrease lipid peroxidation in different tissues [8,13,19,21–23]. Many explanations were offered; on the basis of its chemical structure, propofol behaves in a similar manner to vitamin E by binding to cell membranes or their phospholipids, reacting with the peroxylipid radicals that are formed when lipid peroxidation begins, and by giving rise to a stable phenoxy radical stopping the propagation of lipid peroxidation in the cell membrane [11].

Other studies on antioxidant defensive cell enzyme systems suggested that, at clinically relevant doses, apart from inhibiting lipid peroxidation, propofol may also act on enzyme systems (in particular on the glutathione system), which would lead to a decrease in the activity of glutathione peroxidase and an increase in the activities of glutathione reductase and glutathione transferase – an effect that would yield an increase in cellular reduced glutathione, and hence an increase in defensive cellular antioxidant properties, thereby protecting tissues from oxidative stress [13,22].

Propofol protection may be attributed to its action as a scavenger of peroxynitrites free radical preventing or decreasing their virulent effect [14]. This is achieved through a reduction in neutrophil infiltration, reflected in the lower activity of kidney myeloperoxidase after reperfusion [4]; however, no possible mechanism of action through which this might occur was offered [2]. Neutrophils play a crucial role in the propagation of the damage caused by ischemia, and above all by reperfusion, through the release of oxygen free radicals and proinflammatory cytokines [20,24,25]. Among them, TNF-α and IL-1β are able to induce iNOS expression in different types of cells [26–28], with an excessive production of nitric oxide (NO). The role of NO in I/R syndrome is controversial, but its cytotoxic effect is believed to be because of the formation of peroxynitrites generated when NO is combined with SOA. Furthermore, NO is a potent vasodilator, and it is known that the re-establishment of blood flow to ischemic tissues may exaggerate the tissue lesion, leading to reperfusion injury. The decrease in cytokine levels in patients anesthetized with propofol leads to reduced activation of iNOS in reperfusion, reduced release of NO, less vasodilatation, less neutrophil infiltration, and reduced peroxynitrite formation, resulting in less extensive tissue injury. Accordingly, propofol reduction of peroxynitrites formation could be explained on the basis of either reduced activation of iNOS or reduced production of SOA [29,30]. In addition, TNF-α is a potent inducer of SOA release by other neutrophils, which would increase damage

to endothelial cells, favoring a greater migration of neutrophils [31].

An important suggestion was made by Corcoran *et al.* [12], whereby propofol's beneficial antioxidant properties appear to be independent of its solvent (Intralipid) rather attributed to the active principle of the drug. Certain immunomodulatory effects of propofol, such as suppression of respiratory bursts of neutrophils, may be caused by Intralipid, whereas other actions, such as the ability to scavenge free radicals, appear to be a property of propofol itself [11,23,32].

In contrast, a study comparing both drugs in humans showed a superior cardioprotective effect of sevoflurane in reperfusion injury, which was attributed to its free radical scavenging properties [31]. In addition, serum levels of lactate and pyruvate were found to be higher in group P when both drugs were compared as a preconditioning to protect against reperfusion injury before tourniquet in lower limb surgeries, favoring the use of sevoflurane [33].

Other studies failed to demonstrate a protective effect of propofol on myocardial function during I/R injuries [34,35] and to elicit an antioxidant property for propofol on the oxidative state of T cells [36].

Limitations of the study are lack of references investigating the effects of anesthetic drugs in I/R injuries in human kidney and lack of specificity of TNF-α and IL-1β as indicators of renal ischemia, although being indicators of systemic inflammatory reaction.

We would recommend a wider range of studies that include larger numbers of patients and an expanded serial enzymatic profile as well as plasma drug level analysis using high-performance liquid chromatography to evaluate and correlate the plasma drug level as against the oxidative stress biomarker level. Pharmacokinetic studies can be of great benefit to explain the antioxidant enzyme kinetics during anesthesia.

In conclusion, the use of propofol in patients undergoing aortic aneurysm surgeries with aortic cross-clamping might have favorable effects over sevoflurane in decreasing renal ischemia and systemic inflammatory response as reflected on serum creatinine and plasma TNF-α and IL-1β levels.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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