Thiopental versus ketamine for induction of anesthesia in septic shock: a randomized controlled trial

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Background
Induction of anesthesia in patients with septic shock might result in deleterious hypotension. The aim of this work is to compare low-dose thiopental versus ketamine for induction of anesthesia in patients with septic shock.
Patients and methods
In this randomized controlled double-blinded trial, we included 26 patients with septic shock scheduled for emergency operations under general anesthesia. According to the induction protocol, patients were divided into thiopental group (received thiopental 2 mg/kg+fentanyl 0.5 μg/kg+midazolam 0.05 mg/kg), and ketamine group (received ketamine 1 mg/kg+fentanyl 0.5 μg/kg+midazolam 0.05 mg/kg). Both groups were compared according to mean arterial pressure, cardiac output, heart rate, vasopressor requirements, and incidence of postinduction hypotension.
Results
Both groups were comparable in demographic data. No significant differences were reported between both groups based on mean arterial pressure, cardiac output, and heart rate; however, ketamine group showed higher incidence of postinduction hypotension [11/13 (85%) vs. 5/13 (39%) patients, P=0.041] compared with thiopental group.
Conclusion
Both study regimens, thiopental-based regimen and ketamine-based regimen, showed equivalent hemodynamic effects when used for induction of anesthesia in patients with septic shock. However, thiopental-based regimen was less likely associated with postinduction hypotension.

Keywords:
anesthesia, ketamine, septic shock, thiopental

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Introduction

Patients with septic shock commonly undergo surgical procedures. As these patients are characterized by refractory hypotension [1], induction of anesthesia in such population might lead to deletrious hypotension. Most of the intravenous induction agents have a negative effect on arterial blood pressure and cardiac output [2,3]. Theoretically, the ideal emergency induction intravenous anesthetic should achieve rapid hypnosis and maintain the hemodynamic stability [3].

Ketamine has been reported as an induction anesthetic with a sympathomimetic activity [3]. In patients with intact autonomic nervous system, ketamine increases heart rate, cardiac output, and arterial blood pressure [2]. Despite its sympathomimetic activity in hemodynamically stable patients, the hemodynamic response to ketamine in unstable cardiovascular conditions is not clear. In-vitro studies showed that ketamine exerts a direct dose-dependent negative inotropic effect on human cardiac muscles [4]. Animal studies showed controversial results for the cardiovascular effects of ketamine in different models of shock [5–7]. Evidence about the best protocol for induction of anesthesia in shocked patients is mainly based on case series [8,9].

This randomized controlled trial compared two protocols (ketamine-based vs. thiopental-based) for induction of anesthesia in patients with septic shock aiming to reach the more stable protocol on patients' hemodynamics.

Patients and methods

This randomized controlled double-blinded study was conducted in Cairo University Hospital after research ethics board approval (N-22-2017). The study was

registered at clinicaltrials.gov registry system before patient recruitmement (NCT03104140; date of registraion: April 7, 2017). Written informed consent was obtained from participants or their surrogates before enrollement. Randomization was achieved using a computer-generated sequence. Concealment was achieved using opaque envelopes.

Included patients were patients with septic shock [defined as adult patients with hypotension requiring vasopressor therapy to maintain mean arterial pressure (MAP) above 65 mmHg and elevated serum lactate (above 2 mmol/l) despite adequate fluid resuscitation in addition to the presence of infection [1], aged between 16 and 65 years scheduled for emergency surgery. We excluded patients with traumatic brain injury and patients with history of cerebrovascular disorders.

Patients were resuscitated preoperatively according to surviving sepsis campaign guidelines [10]. An initial bolus of 30 ml/kg crystalloid solution was infused. Following the initial fluid bolus, crystalloids were infused according to fluid responsiveness guidelines [11]. In nonfluid-responders, norepinephrine infusion was initiated to maintain MAP above 65 mmHg.

Patients were monitored using ECG, pulse oximetry, and invasive and noninvasive blood pressure monitors. Cardiac output was obtained using noninvasive electrical cardiometry ICON monitor (Osypka Medical Inc., La Jolla, California, USA, and Berlin, Germany). The monitor was connected to the patient through four ECG electrodes, which were placed in the following sites: (a) at the left neck below the ear; (b) directly above the midpoint of the left clavicle; (c) along the left mid-axillary line at the level of the xiphoid process; and (d) two inches caudad from the third electrode.

Before induction of anesthesia, patients were randomized into two groups:

(1) Ketamine group (n=13): in these patients, anesthesia was induced by intravenous ketamine (1 mg/kg)+fentanyl 0.5 μg/g+midazolam (0.05 mg/kg).
(2) Thiopental group (n=13): in these patients, anesthesia was induced by intravenous thiopental sodium (2 mg/kg)+fentanyl 0.5 μg/kg+midazolam (0.05 mg/kg).

The study drugs were prepared by a research assistant in a covered syringe to ensure that the treating physician was blinded to the color of the drug. Inability to respond to a simple verbal order was considered the end point for hypnosis [12]. Endotracheal intubation was achieved in both groups aided by succinylcholine (1 mg/kg intravenous). Atracurium was administered for maintenance of muscle relaxation at a dose of 0.5 mg/kg followed by 10-mg increments. Patients were mechanically ventilated at tidal volume of 6–8 ml/kg. Respiratory rate was adapted to maintain end-tidal CO_2 between 30 and 35 mmHg. Postinduction hypotension (defined as decreased MAP by 20% or more from the baseline reading) was managed by increasing norepinephrine infusion rate. Maintenance of anesthesia was achieved by isoflurane titrated to keep MAP above 65 mmHg.

Outcomes

Our primary outcome was change in MAP. MAP was continuously measured using invasive blood pressure monitor connected to radial arterial catheter. MAP was recorded at the baseline (before induction of anesthesia) and every minute after induction of anesthesia for 30 min Analyzed MAP values included the baseline reading followed by 1-min interval readings for 6 min, and then 2-min interval readings till 14 min after induction.

Other outcomes included the following:

(1) Number of patients with postinduction hypotension. A patient was considered to have postinduction hypotension if MAP decreased by 20% from the baseline value and required initiating or increasing the rate of norepinephrine infusion, and/or decreasing the concentration of isoflurane.
(2) Other hemodynamic data: heart rate, cardiac output, and systemic vascular resistance. Data were recorded through ECG monitor and electrical cardiometry. Analyzed hemodynamic data included the baseline reading (before induction of anesthesia) followed by 1-min interval reading after induction of anesthesia for 6 min, and then 2-min interval reading till 14 min after induction.
(3) Duration of hypotension.
(4) Serum lactate: baseline reading and 14-min postinduction reading.
(5) Fluid infusion, blood transfusion, urine output, and intraoperative losses.
(6) Demographic data (age, sex, and history of chronic illness).

Sample size calculation and statistical analysis

Our primary outcome was MAP 1 min after induction of anesthesia. We performed a pilot study on eight patients with septic shock. MAP 1 min after induction

of anesthesia using ketamine was 55±4 mmHg. We calculated a conservative sample size that could detect a mean difference of 10% (i.e. 5.5 mmHg) between the study groups. Using MedCalc Software version 14 (MedCalc Sofware bvba, Ostend, Belgium), a sample size of 18 patients (nine patients per group) was needed to have a study power of 80% and alpha error of 0.05. The number was increased by 20% to compensate for possible dropouts.

Statistical package for social science (SPSS) software, version 15, for Microsoft Windows (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. Categorical data were presented as frequency (%) and were analyzed using χ^2 test. Continuous data were tested for normality using Shapiro–Wilk test and presented as either mean (SD) or median (quartiles) as deemed appropriate. Continuous data were analyzed using unpaired *t* test (for normally distributed data) and using Mann–Whitney test on ranks (for skewed data). For repeated measures, general linear model was used to run mixed analysis of variance (within-between subject factors). Post-hoc pairwise comparison was performed using Bonferroni test. *P* value less than or equal to 0.05 was considered statistically significant.

Results

A total of 41 patients were evaluated for eligibility for the study; 15 patients were excluded (10 patients did not meet the inclusion criteria and five patients declined to participate). Therefore, 26 patients were randomized to receive one of the two interventions, and all the patients were available for final analysis (Fig. 1). Demographic data and baseline characteristics were comparable between both study groups (Table 1).

Hemodynamic variables (MAP, CO, heart rate, and systemic vascular resistance) were comparable between both study groups (Figs 2–4). The rate of norepinephrine infusion was generally increased in both groups compared with the baseline infusion rate. However, the number of patients with significant postinduction hypotension was higher in ketamine group compared with the thiopental group [11 (85%) vs. 5 (39%) patients; *P*=0.041] (Table 2). The duration of hypotension was more likely shorter in thiopental group compared with ketamine group without reaching statistical significance (Table 2).

Discussion

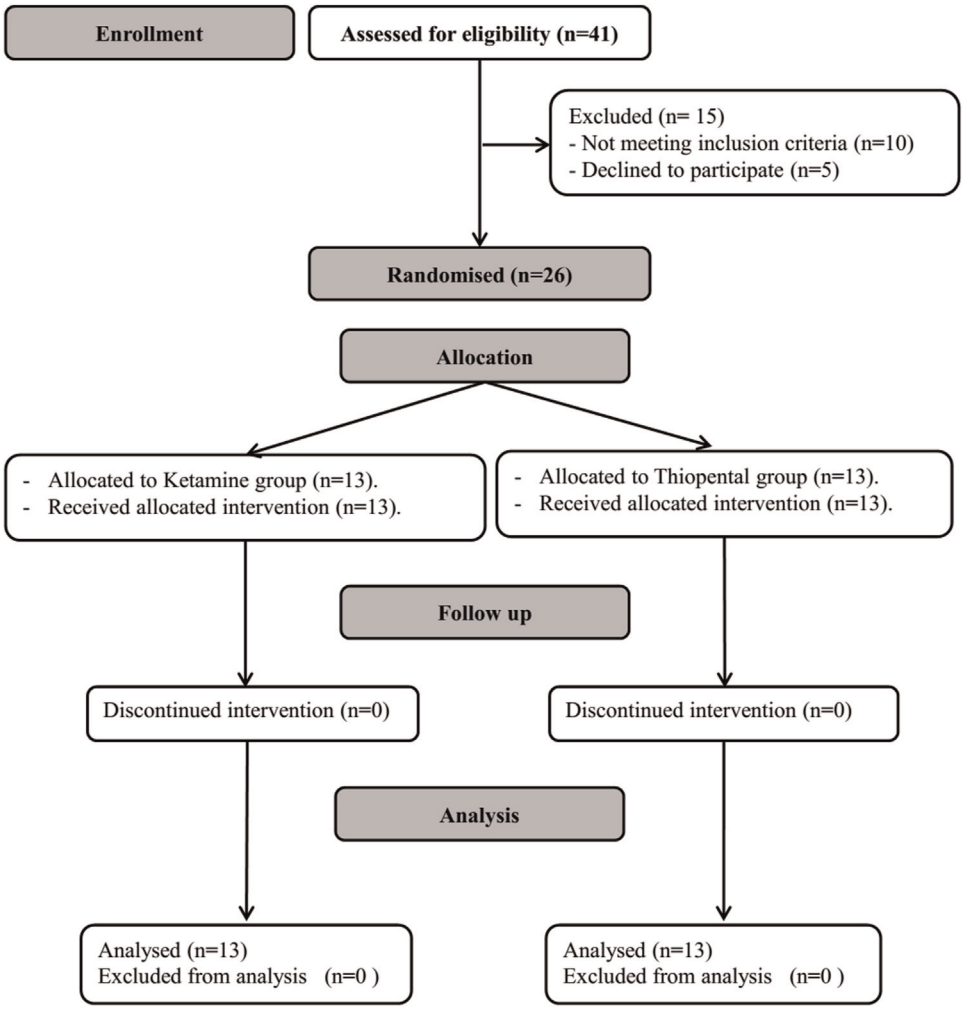
We reported that using thiopental-based regimen was associated with more stable hemodynamic profile compared with ketamine-based regimen for induction of anesthesia in patients with septic shock. Although our records showed comparable blood pressure and cardiac output readings in both groups, the number of patients who experienced postinduction hypotension was higher in ketamine group.

To the best of our knowledge, this is the first study that prospectively and randomly compares two protocols for induction of anesthesia in hemodynamically unstable patients. As recruitment of this type of patients is relatively difficult, most of the available data for induction of anesthesia in this population are based on either animal studies, in-vitro studies, or case series.

Comparison of the cardiovascular effects of different induction anesthetic agents in hemodynamically stable patients showed superiority for ketamine over other agents [2]. Volunteer studies reported that ketamine increased cardiac output by 40–50% [13,14]. Thus, it had been believed that ketamine would be a safe agent for induction of anesthesia in high-risk patients [15]. However, this belief was not supported by clear evidence. In our patients, ketamine showed a negative cardiovascular profile. Two in-vitro studies supported our findings: Sprung and colleagues observed a direct negative inotropic effect for ketamine on human failing and nonfailing heart muscle fibers, and Hanouz *et al.* [16] reported that ketamine exerted a negative inotropic effect on isolated atrial muscle in the presence of beta blockade. Ketamine was associated with negative cardiovascular profiles in critically ill patients [8], as well as catecholamine-dependent heart failure patients [9]. All the available data for ketamine in vulnerable patients are extracted from case series. Thus, it had been recommended that ketamine should be used with caution in hemodynamically vulnerable patients till the presence of randomized controlled trials [8,9].

The discrepancy between the hemodynamic effect of ketamine in stable and nonstable hemodynamic conditions might be explained by the mechanism of action. Ketamine increases cardiac output owing to sympathetic stimulation and not owing to direct inotropic effect [17]. Thus, the effect of ketamine would be different if the sympathetic system was blocked [6,17] or maximally stimulated [8]. Patients with septic shock are characterized by marked preoperative stress that would alter their response to ketamine; this might be the cause of the negative hemodynamic response to ketamine. In line with this explanation, Christ *et al.* [9] had reported that ketamine exerts a negative hemodynamic effect in patients with

Figure 1



CONSORT chart showing patient recruitment.

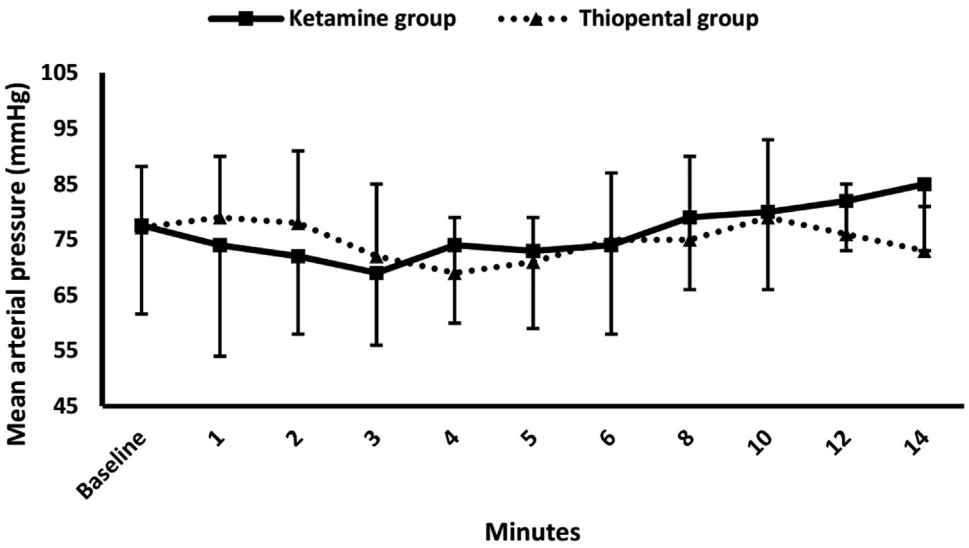
Table 1 Demographic data and baseline characteristics

	Ketamine group (*N*=13)	Thiopental group (*N*=13)	*P* value
Age (years)	42 (16)	52 (17)	0.18
Male sex	7 (54)	7 (54)	1
Source of sepsis			
Abdominal	10 (77)	7 (54)	0.41
Other	3 (23)	6 (46)	
Hemoglobin (g/dl)	11.1 (3.7)	10.9 (1.8)	0.95
Prothrombin concentration	57 (10)	62 (15)	0.39
Urea (mg/dl)	77 (45)	97 (54)	0.32
Creatinine (mg/dl)	1.5 (1, 3.5)	1.3 (0.75, 3.8)	0.96
Baseline respiratory rate (per minute)	30 (8)	30 (6)	0.96
Baseline heart rate (per minute)	118 (22)	110 (18)	0.33
Baseline cardiac output (l/min)	8.6 (2.9)	8.2 (2.4)	0.74
Baseline mean arterial pressure (mmHg)	78 (16)	77 (11)	0.95
Baseline norepinephrine infusion rate (μg/ min)	13 (0, 15)	11 (0, 15)	0.66
Number of patients on vasopressor infusion before induction	7 (54)	9 (69)	0.69
Central venous oxygen saturation	57 (15)	62 (15)	0.37

Data are presented as mean (SD), median (quartiles), and *n* (%).

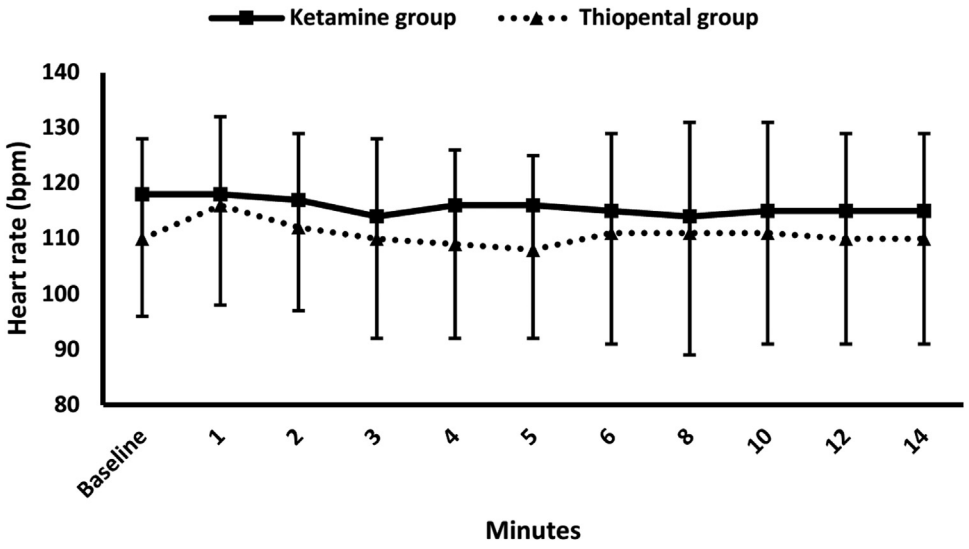
catecholamine-dependent heart failure. Miller *et al*. [18] had reported that ketamine exhibits blunted hypertensive response and more frequent hypotension in out-of-hospital patients with high shock index. In an in-vitro study, although Hanouz *et al*. [16] found that ketamine induced a positive inotropic effect on isolated

Figure 2



Mean arterial pressure. Markers are means, and error bars are standard deviations.

Figure 3



Heart rate. Markers are means, and error bars are standard deviations.

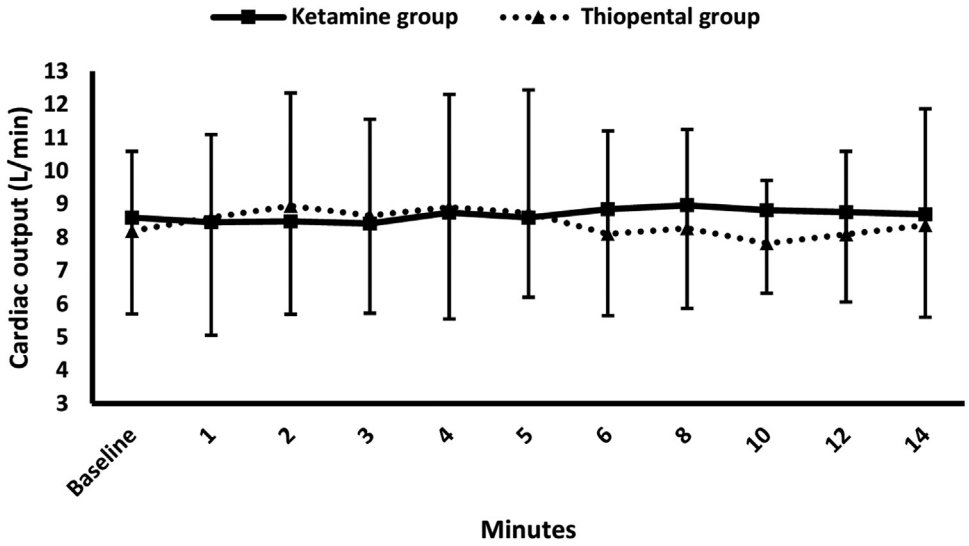
atrial muscle, they reported a negative inotropic effect in the presence of beta blockade.

The cardiovascular effects of ketamine in animal studies were controversial. Ketamine maintained hemodynamic profile in experimental hemorrhagic shock as well as experimental septic shock [19]. However, ketamine depressed myocardial contractility in chronically instrumented dogs with autonomic nervous system blockade [7]. Most of the available data were based on comparing ketamine with inhalational anesthetic agents [6,19] or with etomidate [5]. None of them compared ketamine with thiopental. Moreover, none of these studies used the combination of the induction agent with opioids and benzodiazepines as we did in our patients.

Jabre *et al*. [20] had compared ketamine with etomidate in induction of anesthesia in critically ill patients. Jabre and colleagues reported that ketamine was a safe induction agent in critically ill patients; however, shocked patients in their study were only 11%. No subgroup analysis was reported in the study by Jabre and colleagues to describe the hemodynamic effects of both agents in shocked patients.

Thiopental is a frequently used agent for induction of anesthesia. In the commonly used doses, thiopental is

Figure 4



Cardiac output. Markers are means, and error bars are standard deviations.

Table 2 Patient outcomes and norepinephrine consumption

	Ketamine group (*N*=13)	Thiopental group (*N*=13)	*P* value
Serum lactate (baseline) (mmol/dl)	4.1 (1.7)	3.2 (1.5)	0.21
Serum lactate (after 14 min) (mmol/dl)	2.7 (2.1, 3.9)	2 (1.7, 3.3)	0.17
Patients with postinduction hypotension	11 (85)	5 (39)	0.041
Duration of hypotension (min)	4 (0, 7.5)	0 (0, 3)	0.09
Total 10-min norepinephrine requirements (μg)	160 (0, 453)	128 (37, 227)	0.61

Data are presented as mean (SD), median (quartiles), and *n* (%).

characterized by vasodilatation and hypotension [3,21]. It had been recommended to avoid using larger doses of thiopental (above 3 mg/kg) in hemodynamically compromised patients [3]. In our patients, we used a cocktail that includes a low dose of thiopental, fentanyl, and midazolam. We hypothesized that using such low doses would maintain cardiovascular stability. Comparing thiopental and ketamine as induction agents had been previously reported in only two trials: the first trial was conducted in stable, normotensive patients [2], whereas the second trial was conducted in healthy pregnant women undergoing cesarean delivery [22]. Thiopental showed acceptable hemodynamic profile when compared with propofol in elderly patients [23]. To the best of our knowledge, this is the first randomized controlled trial comparing both agents in patients with septic shock. This is also the first randomized controlled trial comparing two induction protocols in humans with shock.Patients with septic shock are usually characterized by refractory hypotension [1], which is aggravated during anesthesia [24]. In addition to the negative cardiovascular effect of most induction agents, switching from negative thoracic pressure to positive pressure after endotracheal intubation leads to decreased venous return, and consequently decreasing left ventricular preload [24]. Moreover, positive intrathoracic pressure leads to increased pulmonary vascular resistance and decreased right ventricular ejection fraction [25]. Moreover, septic shock in some patients is associated with myocardial dysfunction [26]. According to all these factors, induction of anesthesia in patients with septic shock could result in major cardiovascular sequelae, which necessitates meticulous choice of the induction anesthetic agent.

Our study had some limitations: first, it is a single-center study. Second, we included patients with septic shock; thus, we could not extrapolate our findings to other types of shock. Third, we used a combination of induction agent, opioid, and benzodiazepine. Other combinations of induction agents need to be investigated in this population. Different doses also need to be investigated. Fourth, we did measure the lactate in early stage while not affected by the postinduction hypotension as the level of lactate would take much more time to be affected.

Conclusion

In conclusion, both study regimens, thiopental-based regimen and ketamine-based regimen, showed equivalent hemodynamic effects when used for induction of anesthesia in patients with septic shock. However, thiopental-based regimen was less likely associated with postinduction hypotension.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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