Sevoflurane Preconditioning and Total Knee Arthroplasty Bleeding: A Randomized Controled Trial

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Research Article

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Abstract

Background: Total knee arthroplasty (TKA) is a highly complex and effective surgery even though its perioperative bleeding may increase the need for blood transfusion and its associated infection risk, cardiovascular overload, increased costs, and mortality. As tourniquet reduces intraoperative bleeding it may be associated with postoperative bleeding, venous thrombosis, and distal ischemia. The reperfusion may trigger a local and systemic inflammatory response. Anesthetic preconditioning (APC) with sevoflurane minimizes ischemia-reperfusion syndrome (I/R). This study evaluated the effects of APC with sevoflurane on perioperative bleeding in TKA.

Methods: We allocated 30 patients into two groups: a sevo group (sevoflurane 2% for 15 minutes before the tourniquet) and a control group (propofol infusion). Laboratory tests were collected right before the tourniquet (LAB PRE, in the operating room) and after its release at four moments: LAB POST (immediately after), LAB 2 (two hours after), LAB 12 (12 hours after), and LAB 24 (24 hours after). The volume of the suction drain was measured at one, two, 12, and 24 hours after the end of the surgery. Antifibrinolytics were not administered.

Results: There was no statistically significant difference in bleeding-related variables, such as drained volume and hemoglobin and hematocrit measurements. Drainage volume was higher in the first two hours after the procedure, while hematocrit decreased pre- to post-operatively and between two- and 12-hours post-procedure.

Conclusion: Sevoflurane as an anesthetic preconditioning did not reduce postoperative bleeding in TKA surgery.

Trial Registration: ClinicalTrials.gov – NCT03379103; December 20, 2017.

Background

Knee osteoarthritis affects about 37% of those over 60 years of age, causing severe pain and impairing basic activities, with high therapeutic and social costs.[1] Total knee arthroplasty (TKA) is the established treatment for advanced cases with low perioperative mortality. It provides functional improvement and a return to daily activities. TKA perioperative bleeding is an important complication which increases the need for blood transfusion, the infection rate, hospital stays, and costs. [2, 3]

Most of these procedures are performed with pneumatic tourniquets for a bloodless surgical field and more suitable prosthesis cementation conditions. Ischemia distal to the withers creates tissue hypoxia and anaerobic metabolism. Post-reperfusion, cytokines and free radicals are produced, especially reactive oxygen species (ROS). This ischemia-reperfusion syndrome (I/R) triggers a local and systemic inflammatory response. [4,5] Locally, I/R increases fibrinolysis, impairs platelet adhesion, and promotes leukocyte migration associated with pulmonary, hepatic, renal, and brain changes. [5,6]

A protective effect of ischemic preconditioning (IPC) has been suggested,[7] while a similar effect occurred when halogenated anesthetics were administered before definitive ischemia, mimicking IPC.[8] Sevoflurane modulates the neuroinflammation induced by cerebral I/R, preserves myocardial function in coronary surgery, and attenuates the hemodynamic response in reperfusion injury. [9,10]. An experimental model of renal injury suggested superior protective effect for isoflurane compared to repeated ischemic preconditioning.[11]

A recent review found that skeletal muscle I/R reduces protein synthesis, increases protein degradation, and upregulates genes in cell stress pathways, increasing local and systemic oxidative stress and inflammatory reactions. Propofol, IPC, and vitamin C showed protective effects, but no relationship between biochemical parameters and clinical outcomes could be validated.[12]

This study aimed to determine whether sevoflurane as an anesthetic preconditioning agent reduces bleeding after muscular ischemia-reperfusion in patients undergoing total knee replacement. The primary outcome was blood loss in the immediate postoperative period, for up to 24 hours.

Methods

This study included patients with unilateral TKA who were older than 18 years of age and classified as ASA I or II (American Society of Anesthesiologists physical status). The surgeries were performed at IOT HCFMUSP between February and December of 2018.

Patients were excluded if they were diagnosed with grade II obesity according to body mass index (BMI) higher than 35 kg/m^2, had renal failure (serum creatinine > 1.4 mg/dL or on a dialysis program), myocardial infarction, unstable coronary disease in the six months before surgery, severe liver or gastrointestinal disorders, neuropathic diseases, diabetes, psychiatric disorders, were pregnant or lactating, or were smokers. Patients with hematocrit (Ht) levels below 30% or hemoglobin (Hb) levels below 10g/dL, with a history of coagulation disorders, or who used anticoagulants or antiplatelet agents in the five days before surgery were also excluded.

In this prospective, randomized study, we recorded patients' age, BMI, sex, and ASA status. Subjects were assigned into one of two groups by a random number table. The control group did not receive any intervention as preconditioning, while the sevoflurane group participants received 2% sevoflurane for 15 minutes before limb ischemia by a pneumatic tourniquet. The primary outcome was the volume of blood drainage in the postoperative period.

Electrocardiography (ECG), oxygen saturation (SpO2), and noninvasive blood pressure measurements were recorded throughout the surgery. An 18-gauge intravenous catheter was inserted in the upper limb to administer a lactate solution (10 mL/kg) followed by midazolam (0.05 mg/kg) and prophylactic antibiotic therapy with cefoxitin (1.5g). Patients then received spinal anesthesia with a 27G Whitacre needle inserted through the L4-L5 intervertebral space. We injected 20 mg of 0.5% isobaric bupivacaine and 100 µg of morphine. After the spinal anesthesia, patients were placed in the supine position to

receive general anesthesia with propofol (1.5 mg/kg to 2.5 mg/kg), fentanyl (2.5 µg/kg-5 µg/kg), and cisatracurium (0.1mg/kg) followed by an intratracheal tube insertion. Mechanical ventilation was instituted with FiO2 at 40%, PEEP at 5 cm H2O, RR at 10 rpm, tidal volume at 5 mL/kg-7 mL/kg, and new settings to preserve ETCO2 at 35-37 mmHg.

Right after mechanical ventilation was instituted, we administered 2% sevoflurane to the treatment group for 15 minutes, while the control group received a mixture of oxygen and compressed air with 40% FiO2. During this 15-minute interval, a Foley urinary catheter was inserted to quantify the urine output during surgery and for up to 24 hours afterward, and then removed. Volume replacement was maintained at a rate of 5mL/kg/hour, except in cases where there was a drop of 20% or more in baseline systolic blood pressure (SBP), the SBP was less than 90 mmHg, the heart rate (HR) greater than 100 bpm, or urine output was 0.5mL/Kg/h or lower.

All anesthetic procedures were performed by the same anesthesiologist up to discharge from the post-anesthesia care unit (PACU) and were not blinded to randomization. Neither the patient nor the surgical team knew which study group the participants were in (Consolidated Standards of Reporting Trials, CONSORT, Figure1). We exsanguinated limbs with an Esmarch bandage and installed a pneumatic tourniquet on the subjects' thighs with a pressure of 200-300 mmHg after sevoflurane inhalation ended.

We prevented hypothermia with thermal blankets and intravenous heat. Cases of bradycardia [HR<50 bpm] were treated with atropine (0.5 mg- 1 mg in bolus) and hypotension (SBP< 90 mmHg or a decrease ≥ 20% of the initial SBP) with ephedrine (5 mg-10 mg in bolus). Transfusion of blood components in the intraoperative period was indicated only when hemoglobin levels were < 7 mg/dL or in cases of persistent hemodynamic instability, even after volume expansion and use of the vasopressor ephedrine.

After the surgical procedure, patients were extubated, returned to consciousness, and referred to the PACU with the operative suction drain open. This was the milestone for the start of bleeding volume measurement. Prophylaxis for deep vein thrombosis was performed with 40 mg of subcutaneous enoxaparin 12 hours after the end of the surgical procedure. Early walking was also encouraged.

Blood samples were collected at the time of venipuncture in the operating room (LAB PRE), immediately after the tourniquet was released (LAB POS), and two hours (LAB2), 12 hours (LAB12), and twenty-four hours after the tourniquet was released (LAB24). The analysis included measurements of blood and platelet counts, hematocrit, creatinophosphokinase (CPK), urea, creatinine, sodium, potassium, calcium, chlorides, alanine aminotransferase, aspartate aminotransferase, D-dimer, lactate, fibrinogen, glycemia, prothrombin time (TP), international normalized ratio (INR), and activated partial thromboplastin time (APTT)

Postoperative blood loss was defined as the blood volume measured in the suction drain after the end of surgery. The volume of blood collected in the suction drain was measured and discarded at one hour (VOL1), two hours (VOL2), 12 hours (VOL12), and 24 hours (VOL24) after tourniquet release. PACU discharge was granted only after collection of the LAB2 sample, blood volume measurement VOL2, and a

score of 10 in the modified Aldrete-Kroulik evaluation. Participants were followed up until the 30th postoperative day, and morbidity was registered by analyzing medical records and through telephone contact.

A previous study suggested a visible blood loss around 740 mL, while a meta-analysis showed numbers lower to a volume of 480 mL. [13,14] Upon these informations, we based our sample on an educated guess of a standard deviation of 200 mL to reach 12 patients required in each group for a power of 80% and an alpha error of 0.05. The analyses were conducted using SPSS software. The distribution of variables was analyzed using the Shapiro-Wilk test. Normally distributed data were reported as mean ± SD. Non-parametric distributions were reported as a median (minimum and maximum), whereas the categorical variables were represented as frequencies and percentages. A Fisher's exact test was used for comparing categorical variables, and unpaired t-tests or Mann-Whitney tests were used for univariate analysis of continuous variables. The results at determined times, within and between groups, were evaluated using the generalized estimating equation (GEE) with Bonferroni correction. [15] A p value lower than 5% was considered statistically significant.

Results

We analyzed the primary outcomes of eligible patients, and the results are presented in a CONSORT flow diagram (Figure 1). The two groups were comparable for age, BMI, sex, ASA status, operative time, and tourniquet time (Table 1).

Table 1. Demographic data, tourniquet time, hospital staying.

	Sevoflurane (n=16)	Control (n=14)	P-value
Age (years)	64.6 ± 7.9	62.6 ± 7.9	0.5*
Height (cm)	163.8 ± 12.1	162.2 ± 8.6	0.68*
Site (R/L)	8/8	7/7	1.0**
BMI	29.3 ± 36.1	28.0 ± 28.7	0,2*
Sex (M/F)	9/7	6/8	0.7**
ASA (I/II)	3/13	1/13	0.6**
Tourniquet time (min)	197.7 ± 23,0	195.4 ± 26,7	0.8*
Hospital staying (days)	4.2 ± 0.6	4.8 ± 2.7	< 0.5*

R/L: right/left; BMI: body mass index; M/F: masculine/feminine; ASA: American Society of Anesthesiologists functional status classification; min: minutes. *Student t-test; **Fisher exact test.

Bleeding was not significantly different for the sevoflurane group (847,8 ± 450,7) compared to control (974,4 ± 547,2) (mean ± SD). Hb and Ht measurements were reduced in all periods, with a greater decrease in the first two hours and between the two- and 12-hours time point. Laboratory variables were compared for the same period for each group, as well as between every moment within the groups (Table 2). None of the bleeding variables showed a statistically significant difference for any of the observed intervals among the groups.

Table 2. Bleeding volumes measured in the observed periods

	Postoperative periods of measurments			
	VOL1 (1h)	**VOL2 (2h)**	**VOL3 (12h)**	**VOL4 (24h)**
Sevoflurane	212.9 ± 40.9	185.9 ± 46.4	482.5 ± 66.8	177.5 ± 40.5
Control	206.1 ± 48.6	175.7 ± 30.0	371.1 ± 60.9	95.0 ± 19.5
Difference	-6.8 ± 63.5	-10.2 ± 55.2	-111.4 ± 90.4	-82.5 ± 45.0
p-value	0.91	0.85	0.22	0.07

Laboratory analysis of clinical markers as INR, APTT, platelet count, fibrinogen, TP, and D-dimer were not significantly different for any of the observed intervals. Additional laboratory results for renal and liver injury, including hydroelectrolytic balance, CPK, lactate, and glycemic levels were not significant for any of the observed intervals.

The length of hospital stay was similar between the two groups (Table 1), and there was no need for intensive care or deaths in this study. There were some postoperative setbacks, including prolonged antibiotic therapy for two patients in the sevoflurane group and three in the control group. One patient in each group lost their prosthesis, including one episode of deep venous thrombosis in the sevoflurane group. One patient in the control group received a delayed transfusion.

Discussion

This study did not find any difference in blood loss with the preconditioning use of 2% sevoflurane for 15 minutes in patients undergoing TKA using a pneumatic tourniquet. This result may add to the literature of pharmacologic preconditioning however no preventive effect had been reached.[16] It also indicates that preoperative planning with Hb values above 12 g/dL can reduce or even eliminate the need for a postoperative blood transfusion, associated with approaches to address inclusive other identifiable factors.[17,18] Likewise, reduced Hb/Ht levels and the absence of hemodynamic repercussions suggest that a review of mandatory preoperative blood typing is required.[19]

The tourniquet time in this study was longer than expected in both groups, exceeding the average time found in the literature, around 80 minutes.[20] This state could be related to the fact all surgeries were performed by in-training doctors under supervision. A higher bleeding volume could be expected due to

the prolonged duration of tourniquet application in this study.[21, 22] Even though the literature points to factors related to increased bleeding, like the time of ischemia related to a greater production of inflammatory mediators and ROS [23,24], changes in platelet adhesion and increases in fibrinolysis that may occur in a time-dependent manner after I/R altering coagulation[25] the volume measured in this study did not differ from reported previously. The preconditioning with 2% sevoflurane did not result in any comparable effect of blood loss.

Since all patients received propofol to induce general anesthesia and maintain hypnosis throughout the tourniquet procedure and surgery, some residual effects of this agent on the I/R can be considered. Propofol's protective effect has been reported in cases of I/R injury in the heart, brain, and lower limbs. [26-30] More recently, propofol compared with sevoflurane significantly reduced ROS formation on a cellular level and inflammatory cytokines in coronary smooth muscle cells, but not aortic smooth muscle cells.[31]

In clinical practice, tourniquet use, major vascular surgery, and organ transplantation may be related to these mechanisms. Indeed, complement split products and interleucins (IL-6 and IL-8) were found in salvaged blood from the surgical field of hip and knee arthroplasties.[32] As both, propofol and sevoflurane have been reported to protect tissues from I/R injury by reducing oxidative stress and antiinflammatory properties,[33] the results from this investigation could be related to either propofol or sevoflurane or even a synergistic effect related to anti-inflammatory properties[34-37], albeit sevoflurane may show a better protective profile in skeletal muscle I/R.[38]

This study has some limitations. First, the sample came from only one center, even though it is considered a reference in the field. Second, mobility of the knee or first-time walking in the postoperative period were not assessed. Although only one patient received a blood transfusion, his preoperative hemoglobin was 10.2 g/dL and reached 6.7 g/dL on the first postoperative day. This was probably not related to the sevoflurane preconditioning intervention and did not generate a statistical parameter. Finally, the random processing resulted in an unequal number of participants per group (16 and 14), but this did not appear to compromise results or cause an intention-to-treat approach.[39]

Conclusion

In conclusion, Sevoflurane at 2% MAC as an anesthetic preconditioning agent did not reduce postoperative bleeding in the immediate postoperative period of total knee arthroplasty.

Abbreviations

TKA: total knee arthroplasty

APC: anesthetic preconditioning

I/R: ischemia-reperfusion syndrome

IPC: ischemic preconditioning

ROS: reactive oxygen species

IOT: Institute of Orthopedics and Traumatology

HCFMUSP: Hospital das Clínicas, University of São Paulo Medical School

CAPPesq: Ethics Committee for Analysis of Research Projects

ASA: American Society of Anesthesiologists physical status

BMI: body mass index

Ht: hematocrit

Hb: hemoglobina

ECG: electrocardiography

SpO2: oxygen saturation

FiO2: inspired fraction of oxygen

PEEP: positive end expiratory pressure

RR: respiratory rate

ETCO2: end-tidal carbonic dioxide

SBP: systolic blood pressure

HR: heart rate

PACU: post-anesthesia care unit

CONSORT: Consolidated Standards of Reporting Trials

CPK: creatinophosphokinase

SD: standard deviation

GEE: generalized estimating equation

TP: prothrombin time

INR: international normalized ratio

APTT: activated partial thromboplastin time

MAC: minimum alveolar concentration

Declarations

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the Institute of Orthopedics and Traumatology (IOT) of the Hospital das Clínicas, University of São Paulo Medical School (HCFMUSP). The protocol was approved by the HCFMUSP Ethics Committee for Analysis of Research Projects (CAPPesq) and registered at Plataforma Brasil, number CAAE 03735612.7.0000.0068, and ClinicalTrials.gov, protocol NCT03379103 20/12/2017.

All patients were informed verbally, accepted inclusion into the study voluntarily, and approved and signed an informed consent form in accordance with Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

RSAL: designed the study, collected and analysed all data and wrote the manuscript.

RCG: collected all data and analysed wrote the manuscript.

AK: collected all data and wrote the manuscript, presented results at local Science education for undergraduates.

RVSL: prepared and analysed the data, reviewed the manuscript.

MUR: designed the study, collected the data and reviewed the manuscript.

All authors read and approved the final manuscript.

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Authors' information (optional)

none

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Figures

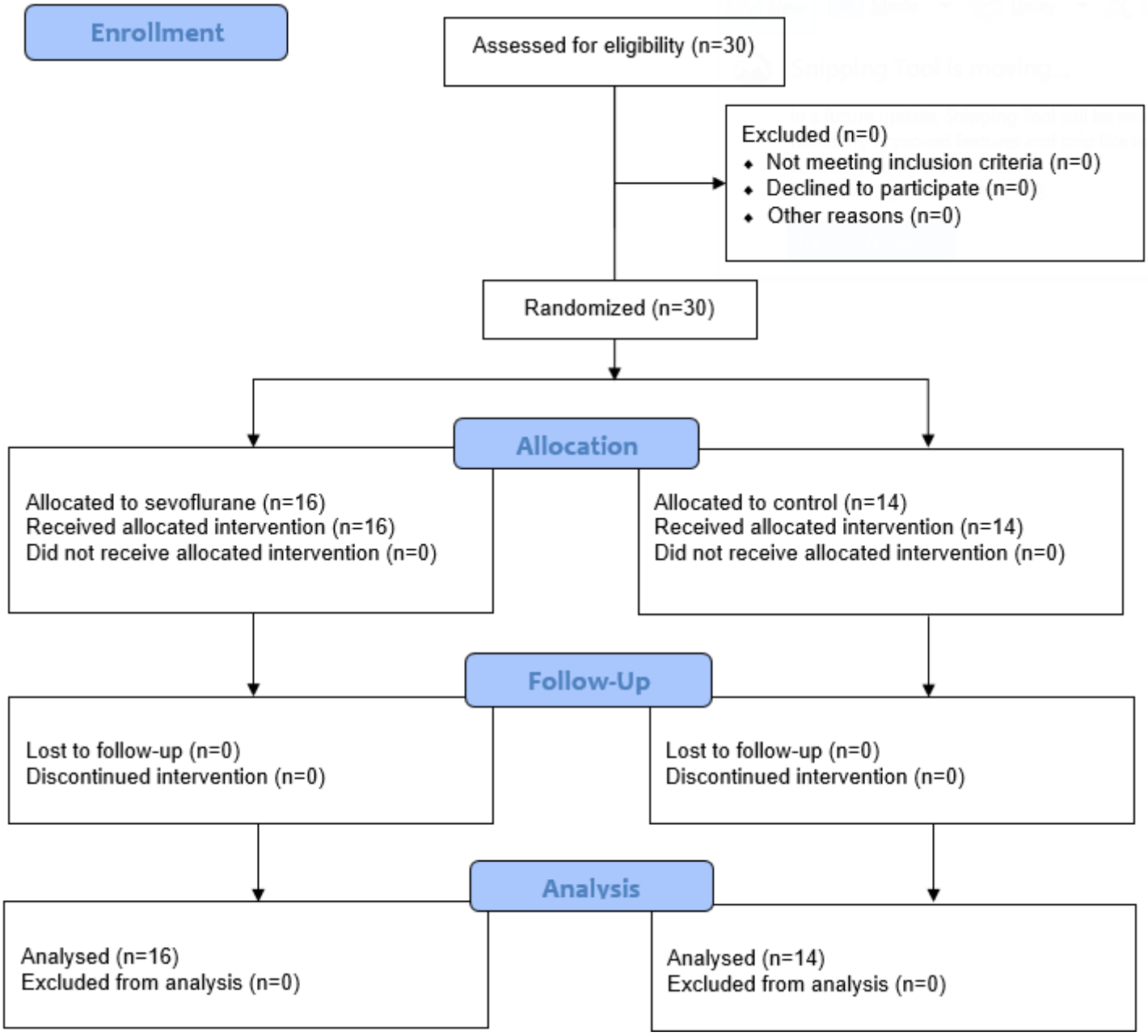

Figure 1

CONSORT Flow Diagram Sevoflurane preconditioning and total knee arthroplasty bleeding