Journal of Biosciences and Medicines, 2023, 11, 254-264
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

# Sevoflurane Preconditioning and Total Knee Arthroplasty Bleeding: Randomized Controlled Trial

**Ricardo S. A. Laurino[1*], Raphael C. Gregnanini[2], Alberto Kanasiro[3], Renata V. S. Laurino[4], Márcia U. de Rezende[5], Joaquim E. Vieira[6]**

[1]Postgraduate Program of Anesthesiology, Surgical Sciences and Perioperative Medicine, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[2]Private Practice, São Paulo, Brazil
[3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[4]Hospital Universitário da Universidade de São Paulo, São Paulo, Brazil
[5]Instituto de Ortopedia e Traumatologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[6]Department of Surgery, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
Email: *kadao@usp.br

**How to cite this paper:** Laurino, R.S.A., Gregnanini, R.C., Kanasiro, A., Laurino, R.V.S., de Rezende, M.U. and Vieira, J.E. (2023) Sevoflurane Preconditioning and Total Knee Arthroplasty Bleeding: Randomized Controlled Trial. *Journal of Biosciences and Medicines*, **11**, 254-264.
https://doi.org/10.4236/jbm.2023.112020

**Received:** January 28, 2023
**Accepted:** February 24, 2023
**Published:** February 27, 2023



## 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 the 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 (IRS). 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 postoperatively and between two and 12 hours post-procedure. **Conclusion:** Sevoflurane as an anesthetic preconditioning did not

reduce postoperative bleeding in TKA surgery.

## Keywords

Arthroplasty, Replacement, Knee, Anesthesia, General; Anesthesia, Spinal, Sevoflurane, Postoperative Hemorrhage

## 1. Introduction

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, infection rate, hospital stays, and costs [2] [3].

Most of these procedures are performed with pneumatic tourniquets in order to provide 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. 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 ischemia-reperfusion, preserves myocardial function in coronary surgery, and attenuates the hemodynamic response in reperfusion injury [9] [10]. An experimental model of renal injury suggested a 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.

## 2. Methods

Participants were screened and recruited at the outpatient clinic 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.

## 2.1. Participants

This study included patients with unilateral total knee arthroplasty who were older than 18 years of age and classified as ASA I or II (American Society of Anesthesiologists physical status). Inclusion criteria were patients able to read who signed a written informed consent form and accepted inclusion into the study voluntarily. 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 10 g/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.

## 2.2. Materials

Electrocardiography (ECG), oxygen saturation (SpO2), and noninvasive blood pressure measurements were recorded throughout the surgery (Philips, Brasil). 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 (1.5 g). Patients then received spinal anesthesia with a 27 G Whitacre needle inserted through the L4 - L5 intervertebral space. We injected 20 mg of 0.5% isobaric bupivacaine and 100 μg of morphine. After 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 (0.1 mg/kg) followed by an intratracheal tube insertion. Mechanical ventilation was instituted with $FiO_2$ at 40%, PEEP at 5 cm $H_2O$, FR at 10 rpm, tidal volume at 5 mL/kg - 7 mL/kg, and new settings to preserve $ETCO_2$ at 35 - 37 mmHg (Dräger Primus, Brasil).

### 2.3. Procedures

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% $FiO_2$. 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 5 mL/kg/hour, except in cases where there was a drop of 20% or more in baseline systolic blood pressure, the systolic blood pressure was less than 90 mmHg, the heart rate greater than 100 bpm, or urine output was 0.5 mL/Kg/h or lower.

All anesthetic procedures were performed by the same anesthesiologist including the discharge from the PACU and were not blinded to randomization. Neither the patient nor the surgical team knew which study group the participants were in. We exsanguinated the 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 [heart rate (HR) < 50 bpm] were treated with atropine (0.5 - 1 mg in bolus) and hypotension [systolic blood pressure (SBP) < 90 mmHg or a decrease ≥ 20% of the initial SBP] with ephedrine (5 - 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 (SC) 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, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, lactate, fibrinogen, glycemia, prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time.

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, the 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.

### 2.4. Analyze Method

A previous study suggested a visible blood loss of around 740 mL, while a meta-analysis showed numbers lower with a volume of 480 mL and SD of 200 mL [13] [14]. Upon this information, we based our sample on a formula (n= [2/(740 - 480)/200)$^2$] × $k_{power}$; n = [2/1, $3^2$] ×10.5: 12.4) to reach the 12 patients required in each group for a power of 90% and an alpha error of 0.05 [15]. The analyses were conducted using SPSS software (IBM, Brasil). 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 median (minimum and maximum), whereas 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 [16]. A p-value lower than 5% was considered statistically significant.

## 3. Results

We analyzed the primary outcomes of eligible patients, and the results are presented in a Consolidated Standards of Reporting Trials (CONSORT) flow diagram (**Figure 1**). The two groups were comparable for age, BMI, sex, ASA status, operative time, and tourniquet time (**Table 1**). No patient was excluded.

Bleeding during the 24 hours period was not significantly different for the control group (847.8 ± 450.7) compared to the sevoflurane (974.4 ± 547.2) (mean ± SD). Hemoglobin and hematocrit 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 between the groups.

Laboratory analysis of clinical markers such as INR, activated partial thromboplastin (APTT), platelet count, fibrinogen, prothrombin time (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, creatinophosphokinase, 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 death in this study. There were some postoperative setbacks, including prolonged antibiotic therapy for two patients

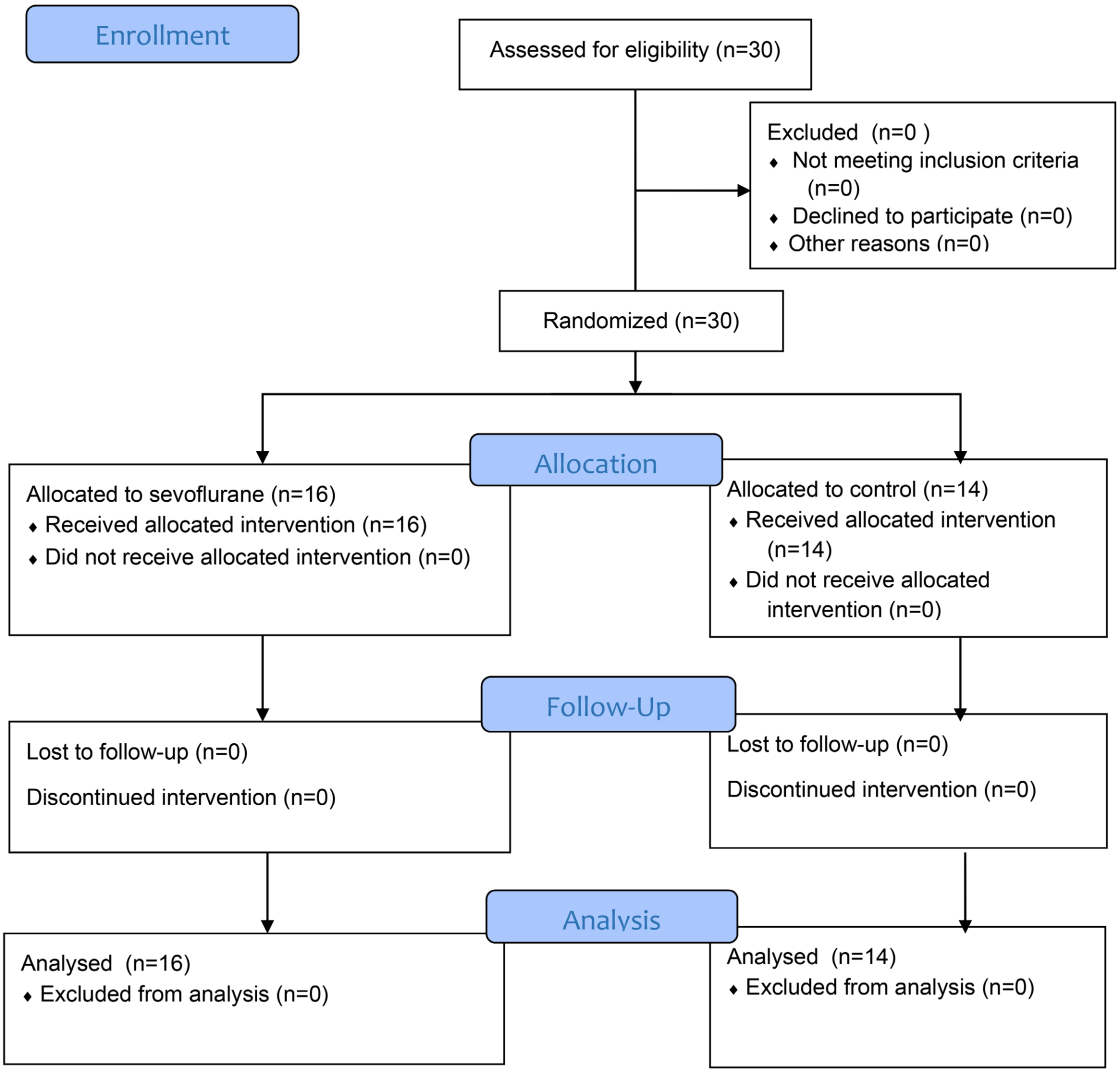


**Figure 1.** CONSORT Flow Diagram. Sevoflurane preconditioning and total knee arthroplasty bleeding.

**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 of operation (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.

**Table 2.** Bleeding volumes measured in the observed periods.

| | Postoperative periods of measurements | | | |
|---|---|---|---|---|
| | **VOL1 (1 h)** | **VOL2 (2 h)** | **VOL3 (12 h)** | **VOL4 (24 h)** |
| 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 |

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.

## 4. 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 during the immediate postoperative 24 hours. This result may add to the literature of pharmacologic preconditioning even though no preventive effect has been reached [17]. It may suggest that preoperative planning where hemoglobin values are above 12 g/dL may postpone the need for postoperative blood transfusion and blood typing [18] [19] [20].

The tourniquet time in this study was longer than expected in both groups, exceeding the average time found in the literature, around 80 minutes [21]. This state could be related to the fact that 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 [22] [23]. 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 reactive oxygen species (ROS) [24] [25], changes in platelet adhesion and increases in fibrinolysis that may occur in a time-dependent manner after ischemia-reperfusion altering coagulation [26], the volume measured in this study did not differ from reported previously. Preconditioning with 2% sevoflurane did not result in any comparable effect on 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 ischemia/reperfusion injury in the heart, brain, and lower limbs [27]-[31]. 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 [32].

In clinical practice, tourniquet use, major vascular surgery, and organ transplantation may be related to these mechanisms. Indeed, complement split prod-

ucts and interleucins (IL-6 and IL-8) were found in salvaged blood from the surgical field of hip and knee arthroplasty [33]. As both, propofol and sevoflurane have been reported to protect tissues from I/R injury by reducing oxidative stress and antiinflammatory properties [34], the results from this investigation could be related to either propofol or sevoflurane or even a synergistic effect related to anti-inflammatory properties [35] [36] [37] [38], albeit sevoflurane may show a better protective profile in skeletal muscle I/R [39].

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 was 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, random processing resulted in an unequal number of participants per group (16 and 14), but this did not appear to compromise the results or cause an intention-to-treat approach [40].

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

## Data Availability

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

## Authors' Contributions

Vieira JE and Laurino RSA conceived and designed the study. Vieira JE and Rezende MU supervised the experimental work, contributed to the acquisition of data, analyzed the data, and wrote and revised the manuscript. Laurino RSA, Gregnanini RC and Kanasiro A participated in the acquisition of data and contributed in writing the manuscript. Laurino RVS participated in the data analysis and contributed in writing the manuscript. All the authors read and approved the final manuscript.

## Acknowledgements

The clinical trial investigators are thankful to the residents in the field of Orthopaedics and the nursing staff for their valuable help in fulfilling this work.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Sharma, L. (2021) Osteoarthritis of the Knee. *The New England Journal of Medi-*

*cine*, **384**, 51-59. https://doi.org/10.1056/NEJMcp1903768

[2] Hu, Y., Li, Q., Wei, B.G., *et al.* (2018) Blood Loss of Total Knee Arthroplasty in Osteoarthritis: An Analysis of Influential Factors. *Journal of Orthopaedic Surgery and Research*, **13**, Article No. 325. https://doi.org/10.1186/s13018-018-1038-0

[3] Kizaki, K., Shanmugaraj, A., Yamashita, F., *et al.* (2019) Total Knee Arthroplasty Using Patient-Specific Instrumentation for Osteoarthritis of the Knee: A Meta-Analysis. *BMC Musculoskeletal Disorders*, **20**, Article No. 561. https://doi.org/10.1186/s12891-019-2940-2

[4] Halladin, N.L., Zahle, F.V., Rosenberg, J. and Gögenur, I. (2014) Interventions to Reduce Tourniquet-Related Ischaemic Damage in Orthopaedic Surgery: A Qualitative Systematic Review of Randomised Trials. *Anaesthesia*, **69**, 1033-1050. https://doi.org/10.1111/anae.12664

[5] Prieto-Moure, B. and Lloris-Carsí, J.M., Barrios-Pitarque, C., Toledo-Pereyra, L.H., *et al.* (2016) Pharmacology of Ischemia-Reperfusion. Translational Research Considerations. *Journal of Investigative Surgery*, **29**, 234-249. https://doi.org/10.3109/08941939.2015.1119219

[6] Guler, N., Burleson, A., Syed, D., *et al.* (2016) Fibrinolytic Dysregulation in Total Joint Arthroplasty Patients: Potential Clinical Implications. *Clinical and Applied Thrombosis/Hemostasis*, **22**, 372-376. https://doi.org/10.1177/1076029615597060

[7] Kalogeris, T., Baines, C.P., Krenz, M. and Korthuis, R.J. (2012) Cell Biology of Ischemia/Reperfusion Injury. *International Review of Cell and Molecular Biology*, **298**, 229-317. https://doi.org/10.1016/B978-0-12-394309-5.00006-7

[8] Murry, C.E., Jennings, R.B. and Reimer, K.A. (1986) Preconditioning with Ischemia: A Delay of Lethal Cell Injury in Ischemic Myocardium. *Circulation*, **74**, 1124-1136. https://doi.org/10.1161/01.CIR.74.5.1124

[9] Lemoine, S., Tritapepe, L., Hanouz, J.L. and Puddu, P.E. (2016) The Mechanisms of Cardio-Protective Effects of Desflurane and Sevoflurane at the Time of Reperfusion: Anaesthetic Post-Conditioning Potentially Translatable to Humans? *British Journal of Anaesthesia*, **116**, 456-475. https://doi.org/10.1093/bja/aev451

[10] Zhong, H., Chen, H. and Gu, C. (2020) Sevoflurane Post-Treatment Upregulated miR-203 Expression to Attenuate Cerebral Ischemia-Reperfusion-Induced Neuroinflammation by Targeting MyD88. *Inflammation*, **43**, 651-663. https://doi.org/10.1007/s10753-019-01147-2

[11] Menting, T.P., Ergun, M., Bruintjes, M.H., *et al.* (2017) Repeated Remote Ischemic Preconditioning and Isoflurane Anesthesia in an Experimental Model of Renal Ischemia-Reperfusion Injury. *BMC Anesthesiology*, **17**, 14. https://doi.org/10.1186/s12871-017-0310-x

[12] Leurcharusmee, P., Sawaddiruk, P., Punjasawadwong, Y., *et al.* (2018) The Possible Pathophysiological Outcomes and Mechanisms of Tourniquet-Induced Ischemia-Reperfusion Injury during Total Knee Arthroplasty. *Oxidative Medicine and Cellular Longevity*, **2018**, Article ID: 8087598. https://doi.org/10.1155/2018/8087598

[13] Sehat, K.R., Evans, R. and Newman, J.H. (2000) How Much Blood Is Really Lost in Total Knee Arthroplasty? Correct Blood Loss Management Should Take Hidden Loss into Account. *Knee*, **7**, 151-155. https://doi.org/10.1016/S0968-0160(00)00047-8

[14] Alcelik, I., Pollock, R.D., Sukeik, M., Bettany-Saltikov, J., Armstrong, P.M. and Fismer, P. (2012) A Comparison of Outcomes with and without a Tourniquet in Total Knee Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *The Journal of Arthroplasty*, **27**, 331-340.

https://doi.org/10.1016/j.arth.2011.04.046

[15] Whitley, E. and Ball, J. (2002) Statistics Review 4: Sample Size Calculations. *Critical Care*, **6**, 335-341. https://doi.org/10.1186/cc1521

[16] Guimarães, L.S.P. and Hirakata, V.N. (2012) Use of the Generalized Estimating Equation Model in Longitudinal Data Analysis. *Revista HCPA*, **32**, 503-511. https://www.lume.ufrgs.br/handle/10183/158366

[17] Lucchinetti, E., Ambrosio, S., Aguirre, J., *et al.* (2007) Sevoflurane Inhalation at Sedative Concentrations Provides Endothelial Protection against Ischemia-Reperfusion Injury in Humans. *Anesthesiology*, **106**, 262-268. https://doi.org/10.1097/00000542-200702000-00013

[18] Themistoklis, T., Theodosia, V., Konstantinos, K. and Georgios, D.I. (2017) Perioperative Blood Management Strategies for patients undergoing total knee replacement: Where Do We Stand Now? *World Journal of Orthopedics*, **8**, 441-454. https://doi.org/10.5312/wjo.v8.i6.441

[19] Mufarrih, S.H., Qureshi, N.Q., Ali, A., *et al.* (2017) Total Knee Arthroplasty: Risk Factors for Allogeneic Blood Transfusions in the South Asian Population. *BMC Musculoskeletal Disorders*, **18**, Article No. 359. https://doi.org/10.1186/s12891-017-1728-5

[20] Birlutiu, R.M., Roman, M.D., Cismasiu, R.S., *et al.* (2017) Sonication Contribution to Identifying Prosthetic Joint Infection with *Ralstonia pickettii*: A Case Report and Review of the Literature. *BMC Musculoskeletal Disorders*, **18**, Article No. 311. https://doi.org/10.1186/s12891-017-1678-y

[21] Rasmussen, L.E., Holm, H.A., Kristensen, P.W. and Kjaersgaard-Andersen, P. (2018) Tourniquet Time in Total Knee Arthroplasty. *Knee*, **25**, 306-313. https://doi.org/10.1016/j.knee.2018.01.002

[22] Muyskens, J.B., Hocker, A.D., Turnbull, D.W., *et al.* (2016) Transcriptional Profiling and Muscle Cross-Section Analysis Reveal Signs of Ischemia Reperfusion Injury Following Total Knee Arthroplasty with Tourniquet. *Physiological Reports*, **4**, e12671. https://doi.org/10.14814/phy2.12671

[23] Xu, H., Yang, J., Xie, J., *et al.* (2020) Tourniquet Use in Routine Primary Total Knee Arthroplasty Is Associated with a Higher Transfusion Rate and Longer Postoperative Length of Stay: A Real-World Study. *BMC Musculoskeletal Disorders*, **21**, Article No. 620. https://doi.org/10.1186/s12891-020-03623-5

[24] Mayer, C., Franz, A., Harmsen, J.F., *et al.* (2017) Soft-Tissue Damage during Total Knee Arthroplasty: Focus on Tourniquet-Induced Metabolic and Ionic Muscle Impairment. *Journal of Orthopaedics*, **14**, 347-353. https://doi.org/10.1016/j.jor.2017.06.015

[25] Arthur, J.R. and Spangehl, M.J. (2019) Tourniquet Use in Total Knee Arthroplasty. *Journal of Knee Surgery*, **32**, 719-729. https://doi.org/10.1055/s-0039-1681035

[26] Watt, J., Ewart, M.A., Greig, F.H., *et al.* (2012) The Effect of Reactive Oxygen Species on Whole Blood Aggregation and the Endothelial Cell-Platelet Interaction in Patients with Coronary Heart Disease. *Thrombosis Research*, **130**, 210-215. https://doi.org/10.1016/j.thromres.2012.03.024

[27] Aldemir, O., Celebi, H., Cevik, C. and Duzgun, E. (2001) The Effects of Propofol or Halothane on Free Radical Production after Tourniquet Induced Ischaemia-Reperfusion Injury during Knee Arthroplasty. *Acta Anaesthesiologica Scandinavica*, **45**, 1221-1225. https://doi.org/10.1034/j.1399-6576.2001.451008.x

[28] Kokita, N., Hara, A., Abiko, Y., *et al.* (1998) Propofol Improves Functional and Metabolic Recovery in Ischemic Reperfused Isolated Rat Hearts. *Anesthesia & Analge-*

*sia*, **86**, 252-258. https://doi.org/10.1213/00000539-199802000-00006

[29] Javadov, S.A., Lim, K.H., Kerr, P.M., *et al.* (2000) Protection of Hearts from Reperfusion Injury by Propofol Is Associated with Inhibition of the Mitochondrial Permeability Transition. *Cardiovascular Research*, **45**, 360-369. https://doi.org/10.1016/S0008-6363(99)00365-X

[30] De La Cruz, J.P., Villalobos, M.A., Sedeño, G., *et al.* (1998) Effect of Propofol on Oxidative Stress in an *in Vitro* Model of Anoxia-Reoxygenation in the Rat Brain. *Brain Research*, **800**, 136-144. https://doi.org/10.1016/S0006-8993(98)00516-2

[31] Yamaguchi, S., Hamaguchi, S., Mishio, M., *et al.* (2000) Propofol Prevents Lipid Peroxidation Following Transient Forebrain Ischemia in Gerbils. *Canadian Journal of Anesthesia*, **47**, 1025-1030. https://doi.org/10.1007/BF03024877

[32] Hsiao, H.T., Wu, H., Huang, P.C., *et al.* (2016) The Effect of Propofol and Sevoflurane on Antioxidants and Proinflammatory Cytokines in a Porcine Ischemia-Reperfusion Model. *Acta Anaesthesiologica Taiwanica*, **54**, 6-10. https://doi.org/10.1016/j.aat.2015.11.002

[33] Andersson, I., Tylman, M., Bengtson, J. and Bengtsson, A. (2001) Complement Split Products and Pro-Inflammatory Cytokines in Salvaged Blood after Hip and Knee Arthroplasty. *Canadian Journal of Anesthesia*, **48**, 251-255. https://doi.org/10.1007/BF03019754

[34] Xu, Z., Yu, J., Wu, J., *et al.* (2016) The Effects of Two Anesthetics, Propofol and Sevoflurane, on Liver Ischemia/Reperfusion Injury. *Cellular Physiology & Biochemistry*, **38**, 1631-1642. https://doi.org/10.1159/000443103

[35] Annecke, T., Kubitz, J.C., Kahr, S., *et al.* (2007) Effects of Sevoflurane and Propofol on Ischaemia-Reperfusion Injury after Thoracic-Aortic Occlusion in Pigs. *British Journal of Anaesthesia*, **98**, 581-590. https://doi.org/10.1093/bja/aem049

[36] Arnaoutoglou, H., Vretzakis, G., Souliotis, D., *et al.* (2007) The Effects of Propofol or Sevoflurane on Free Radical Production after Tourniquet Induced Ischaemia-Reperfusion Injury during Knee Arthroplasty. *Acta Anaesthesiologica Belgica*, **58**, 3-6.

[37] Sánchez-Conde, P., Rodríguez-López, J.M., Nicolás, J.L., *et al.* (2008) The Comparative Abilities of Propofol and Sevoflurane to Modulate Inflammation and Oxidative Stress in the Kidney after Aortic Cross-Clamping. *Anesthesia & Analgesia*, **106**, 371-378. https://doi.org/10.1213/ane.0b013e318160580b

[38] Omer, K., Nermin, G., Ali, A., *et al.* (2017) Tourniquet-Induced Ischaemia-Reperfusion Injury: The Comparison of Antioxidative Effects of Small-Dose Propofol and Ketamine. *Revista Brasileira de Anestesiologia*, **67**, 246-250. https://doi.org/10.1016/j.bjan.2016.10.007

[39] Carles, M., Dellamonica, J., Roux, J., *et al.* (2008) Sevoflurane but Not Propofol Increases Interstitial Glycolysis Metabolites Availability during Tourniquet-Induced Ischaemia-Reperfusion. *British Journal of Anaesthesia*, **100**, 29-35. https://doi.org/10.1093/bja/aem321

[40] Suresh, K. (2011) An Overview of Randomization Techniques: An Unbiased Assessment of Outcome in Clinical Research. *Journal of Human Reproductive Sciences*, **4**, 8-11. https://doi.org/10.4103/0974-1208.82352