


Original Article

A Comparative Study in Influence of Isoflurane and Propofol on IL-1, IL-6, TNF- α Serum Levels after Craniotomy for Supratentorial Brain Tumors

Farhad Safari¹ , Parisa Sezari¹ , Kamran Mottaghi¹ , Bahareh Torbat Isfahani¹, Masoud Nashibi^{1*} 

Abstract

Background: The purpose of this randomized, single-center study was to prospectively investigate the impact of anesthetic techniques for craniotomy on the release of cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor factor-alpha (TNF- α)) and to determine whether intravenous anesthesia compared to inhalational anesthesia attenuates the inflammatory response.

Methods and Materials: The study enrolled 60 patients undergoing craniotomy, allocated into two equal groups to receive either Isoflurane (n=30) and Propofol (n=30). Non-invasive hemodynamic monitoring was used. Serum levels of IL-1, IL-6 and TNF- α were evaluated before and at the end of surgery and anesthesia.

Results: Although there was a significant rise in serum level of inflammatory cytokine but compared with patients anaesthetized with Isoflurane, patients who received Propofol had significant lower levels of IL-1, IL-6 and TNF- α after surgery ($p < 0.05$).

Conclusion: Patients who received Propofol had lower levels of IL-1, IL-6 and TNF- α after surgery. Our findings should incite future studies to prove a potential medically important anti-inflammatory role of Propofol in neuroanesthesia.

Keywords: Craniotomy, Propofol, Isoflurane, Interleukin 1, Interleukin 6, TNF- α

Please cite this article as: Safari F, Nashibi M, Mottaghi K, Sezari P, Torbat Isfahani B. A Comparative Study in Influence of Isoflurane and Propofol on IL-1, IL-6, TNF Serum Levels after Craniotomy for Supratentorial Brain Tumors. J Cell Mol Anesth. 2019;4(1):8-14.

1. Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author: Masoud Nashibi. Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: masoudnashibi@yahoo.com

Introduction

Surgery and anesthesia can be associated with immune system modulation and may affect cell-mediated immune balance and increased risk of postoperative complications such as sepsis and multiple organ damage (1-4). Studies have shown the release of catecholamines as part of the sympathetic

response of the nervous system in a body following surgery and subsequent physiological stresses. Glucocorticoids also are secreted in the same manner during surgery as component of the hypothalamic-pituitary-adrenal axis in the body (5). On the other hand, recent studies have demonstrated that the tissue damage following surgical incision increases the pre-

inflammatory cytokines such as interleukin 1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF- α), in turn enhancing the activity of the hypothalamic-pituitary-adrenal axis and the secretion of glucocorticoids (6, 7).

There is a balance between the release of pro and anti-inflammatory cytokines. Inflammatory reactions that induced by immune cells can cause exacerbation of the pro-inflammatory response and increase the incidence of postoperative complications including; infections, delayed surgical wound healing, cognitive impairment and even progression of malignancies, systemic inflammatory response syndrome (SIRS), also lead to severe hemodynamic disorders and multiple organ failure (8-11).

Human brain is particularly susceptible to oxidative damage compared with other body organs. The brain naturally intakes 20% of the total blood oxygen content and thus the highest levels of oxygen metabolites flow into the bloodstream of the brain. Various studies have shown that exposing the brain to any oxidative stress such as craniotomy can increase brain damage due to the low antioxidant capacity and high levels of oxygen consumed in the brain (12).

Recently it has been confirmed that appropriate anesthetics can modulate the complex reactions of the patient's immune system during major surgery (8). Studies have shown that some injectable and inhaled anesthetics can modulate the immune system response through affecting multiple receptors and ionic channels in leukocytes (13-15).

Propofol has been shown to be one of the most widely used anesthetics in various experimental studies with anti-inflammatory effects. These effects have been seen in other medications, including Isoflurane (16-18). However, various studies have conducted to compare the effects of Propofol and Isoflurane to survey different outcomes. There is a controversy about the degree of effectiveness of these two drugs (19-21).

Considering effects of anesthetics during surgical anesthesia such as craniotomy can be one of the most effective therapeutic strategies against the reduction in the oxidative stress and subsequent complications. Although recent studies have indicated that many anesthetics have anti-inflammatory effects in experimental models, attention has been diverted to their pharmacological and pharmacokinetic aspects in

the use of these drugs and there is no study to verify their effect on inflammatory and antioxidant processes during brain surgery (21). The aim of this study was to compare the influence of intravenous Propofol with Isoflurane anesthesia on plasma concentrations of pro and anti-inflammatory cytokines (IL-1, IL-6 and TNF- α) in patients undergoing craniotomy due to supratentorial tumor surgery.

Methods

After obtaining approval from the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU), this clinical trial was conducted on patients who were candidate for craniotomy (supratentorial brain tumors) referring to Loghman Hakim Hospital, Tehran, Iran. Inclusion criteria included patients 18-65 years, ASA Class I and II, no history of rheumatic diseases or anti-inflammatory drugs.

Exclusion criteria in this study were history of hypersensitivity to the drugs used in the study, patients taking beta-blocker medications or calcium channel blockers and anti-inflammatory vitamin supplements, surgery duration less than an hour, intraoperative need for blood transfusion over four packed cell units.

After selecting patients, explaining the methodology and objectives of the study, written informed consent was obtained from patients and then they were randomly divided into two groups, anesthesia with Propofol and Isoflurane. The study included 60 patients, 20 in the Propofol group and 20 in the Isoflurane group (Figure 1).

Routine supportive interventions such as measuring blood pressure, electrocardiography (ECG) monitoring, measuring peripheral oxygen saturation by pulse oximeter in the operating room were performed for all patients.

After taking the required blood samples and establishing IV line and oxygenation of patients with 100% oxygen for 3 minutes, patients in both groups experienced induction of anesthesia in the following way; Midazolam 0.02 to 0.03 mg/kg, Fentanyl 2 to 6 μ g/kg, Propofol 1 to 5.2 mg/kg, Lidocaine 1 to 5.1 mg/kg, Cisatracurium 0.1 mg/kg. After induction, the anesthesia was maintained using Propofol infusion with a dose of 100 to 200 μ g/kg/min in one group and 2.1% Isoflurane gas for the other group.

The blood pressure and heart rate were decreased to 20% of the baseline level during anesthesia. If the heart rate reached less than 45 bpm, it would be considered as bradycardia and the patients would receive 0.5mg of atropine, if needed.

The intravascular crystalloid fluid was also injected to the patients by reducing the mean arterial pressure to 20% of the baseline level, and if not effective, 5 mg of ephedrine was added.

In this study, 5 mL of venous blood was taken from all patients prior to anesthesia induction and after the completion of surgery in the recovery ward to determine the levels of TNF- α , IL-1 and IL-6 cytokines. The blood samples were transferred to the lab to check the level of interleukins desired and kept at laboratory for about 30 min to form a clot. The serum was then separated by centrifugation at 2500 rpm for 30 min, transferred to plastic test tubes, kept at -20°C to maintain by 6 months and at -70°C to maintain over 6 months. The samples with 0°C temperature were transferred to Immunology Department lab SBMU to assess using ELISA assay (Bender MedSystems GmbH, Campus Vienna Biocenter 2, 1030 Vienna, Austria) measured interleukins with a sensitivity of 0.5 to 1 μ g/l.

Statistical analysis: two-tailed t-test with unequal variances and Chi-square test were used to test the differences in demographic data, duration of the procedure and anesthesia, drug consumption, fluid balance and hemodynamic parameters. Independent T-test was used to compare the differences in cytokines mean values. Results were analyzed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

None of the patients had signs of preoperative infection. All patients underwent craniotomy for the first time because of supratentorial tumor. No significant difference was found between the groups in demographics, underlying pathology, position during surgery, length of hospitalization and intraoperative variables (Tables 1 & 2).

Patients who received Propofol showed statistically significant decrease in IL-1, IL-6 and TNF- α sera level at the end of surgery ($p=0.001$, $p=0.04$ and $p=0.01$) (Table 3).

Discussion

The present study was conducted to compare the effects of Propofol and Isoflurane on the inflammatory cytokines serum levels (IL-6, IL-1 and TNF- α) in patients undergoing craniotomy due to supratentorial brain tumors, showing anesthesia with Propofol significantly reduces serum levels of IL-6, IL-1 and TNF- α compared to Isoflurane.

Cytokines are a group of inflammatory mediators activated in cascades, having stimulatory or inhibitory effects on each other (22). The inflammatory cytokines enter the brain in a variety of ways. These cytokines can cross the blood brain barrier and link to receptors associated with afferent fibers in peripheral nerves. They are also produced in the brain by active microglia, astrocytes and neurons (22, 23).

Some study had results in parallel by our results. Citerio et al. examined the level of neuroendocrine stress response during non-emergency craniotomy and showed that intravascular anesthetics modulated inflammatory responses caused by intraoperative stresses (24). Liu et al. also confirmed a significant decrease in the number of immune cells after induction of anesthesia by intravascular anesthetics in candidates for the craniotomy (11). Marik et al. found that the Propofol was able to decrease the production level of pre-inflammatory cytokines and increase the production of nitric oxide and could prevent neutrophil activity (25). In a study of Ye et al, in vitro use of Propofol completely impeded lipopolysaccharide (LPS)-related activation of microglia and the production of pro-inflammatory cytokines (17).

The present study also revealed that both drugs decreased the studied cytokine levels, but the difference in this decrease was significantly higher in the patients under the anesthesia with Propofol compared to the Isoflurane group. This difference indicates that the Propofol was more effective in controlling inflammation following surgery compared to the Isoflurane. Liu et al. proved the anti-inflammatory effects of the Propofol in animal models (11). Ding et al. also underlined that the Propofol was associated with a decrease in the production of IL-1

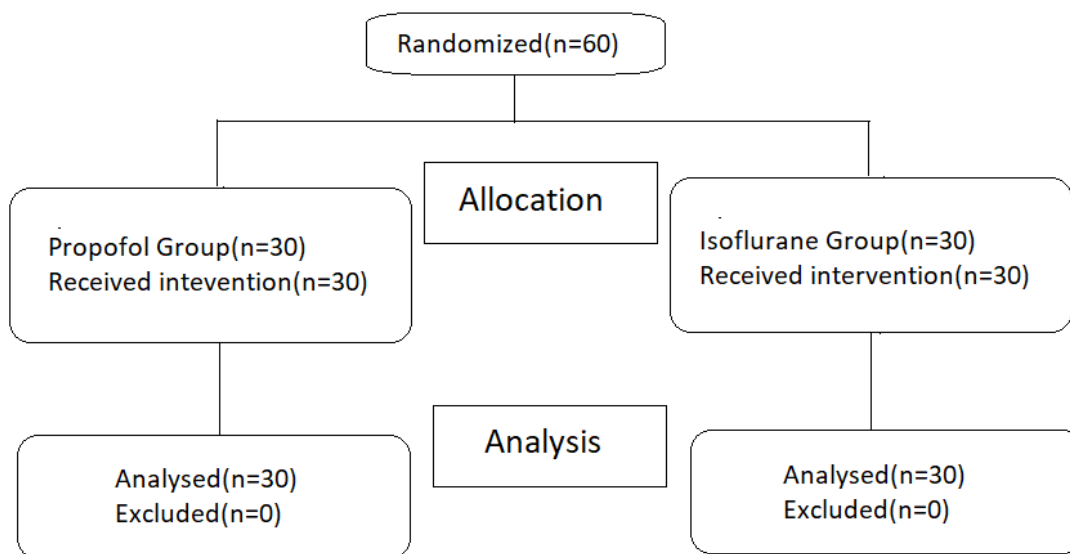


Figure 1. Flow diagram of the study.

Table 1: Baseline demographics and surgical procedure.

	P	I	P value
Age	48.06±5.79	47.80±5.79±	0.85
BMI	25.96±1.7	15.36±1.5	0.17
Gender(M/F)	19/11	13/17	0.19
ASA(I/II)	20/10	15/15	0.29

The results are expressed as mean ± SD or number of patients
 The differences between groups were not significant (p > 0.05)
 ASA: American Society of Anesthesiologists

Table 2: Intraoperative variables.

	P	I	P value
Duration of procedure (min)	213.5±26.5	204.5±16.3	0.11
Duration of anesthesia (min)	230.1±15.7	229±14.5	0.76
Intravenous fluid (ml)	1275±170.7	1180±148.3	0.40
Urine volume (ml)	723±23.3	735±5.0	0.42
Mean systolic Pressure(mm/Hg)	115±7.0	110±8.1	0.50
Mean Diastolic Pressure(mm/Hg)	76.66±5.7	71.66±2.8	0.25

The results are expressed as mean ± SD or number of patients
 The differences between groups were not significant (p > 0.05)

and TNF-α in animal models of brain trauma due to a

decrease in AQP-4 gene expression (26). Sheng et al.

Table 3: Interleukin 1, 6 and TNF α serum levels at the end of surgery

	I	P	P value
IL-1	11426.0 \pm 683.93	8473.25 \pm 733.69	0.001
IL-6	11168.0 \pm 782.0	8028.50 \pm 109.68	0.04
TNF- α	5.98 \pm 1.12	3.62 \pm 0.96	0.01

I: Isoflurane group, P: Propofol group

also expressed that the Propofol in patients undergoing craniotomy following hypertension and intracerebral hemorrhage reduced TNF- α levels in comparison with the control group, as well as the Propofol resulted in a significant decrease in the IL-6 level compared to the control group (27). Berger et al. also stated that the Propofol and the Isoflurane in the patients undergoing craniotomy reduced postoperatively TNF- α level in both groups, but there was no significant difference in the reduction level between the two groups (28).

In-vitro studies have highlighted that the Propofol affects the *HMGB1* gene expression level in macrophage cells by lipopolysaccharides and reduces the release of IL-6 and TNF- α , justifying the anti-inflammatory effects of the Propofol during the craniotomy. The *HMGB1* is a DNA-binding protein that conserves the nucleosome structure and modulates the gene expression. Recent studies have reported that this protein has pro-inflammatory effects during inflammatory responses (29). This protein through activating macrophages helps secreting various inflammatory cytokines, including IL-1, IL-6, TNF- α and nitric acid (30). On the other hand, the effects of Isoflurane on the inflammatory cytokines have been confirmed in the animal models. The animal models showed that 1.4% Isoflurane decrease the level of IL-1, IL-6 and IFN- α (31). Another study stated that 1.4% Isoflurane suppressed TNF- α in the LPS-induced models (32).

However, human models showed contradictory results about the effect of Isoflurane on the inflammatory cytokines. Karabivik et al. claimed that the Isoflurane might be involved in elective abdominal surgery with damage to DNA following inflammatory system activity. In the same way, other studies on patients who undergoing cholecystectomy and hysterectomy found that the Isoflurane could increase inflammatory responses (33-35).

In contrast, and in contradiction to the results of

previous studies, ENT surgical procedures indicated that the Isoflurane had no effect on the level of inflammatory reactions and even reduced the level of IL-6 in some cases (36-38).

Based on the results of recent studies it seems that, the effect of Isoflurane and Propofol is highly dependent on the type of surgery, and it is necessary to select any of these drugs in accordance with the type of surgery.

It is important to note that changes in the level of cytokines from the baseline level can occur due to multiple causes, including various diseases, drug therapies, type of surgery or postoperative complications.

During neurosurgical surgery, the inflammation occurs mainly due to brain damage for several causes, such as brain tissue damage and hemodynamic alteration in the body, which affect the normal structure of the brain (39). Therefore, it is recommended that subsequent studies examine the effect of other background factors affecting the level of inflammatory cytokines.

Conclusion

The results of the current study showed no significant differences between these variables in the two groups of anesthesia. In general, our findings indicated that use of Propofol in the elective craniotomy in treating the supratentorial brain tumors, compared to the Isoflurane, significantly and more effectively modulates the inflammatory responses in the patients, highlighting the neuroprotective effect of this drug during the neurosurgeries.

According to the results, it could be concluded that the anti-inflammatory cytokines, such as IL-1, IL-6 and TNF- α , after surgery showed significantly low increased serum levels in the Propofol-induced anesthesia compared to the Isoflurane-induced anesthesia. This reflects the fact that the Propofol-

induced anesthesia can have anti-inflammatory effects, followed by protective effects on the nervous system.

Acknowledgment

The authors would like to acknowledge the kind help of the personnel of Anesthesiology Research Center, SBMU, Tehran, Iran. Besides, the authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, SBMU, Tehran, Iran for their support, cooperation and assistance throughout the study.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

- Slade MS, Simmons RL, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. *Surgery*. 1975;78(3):363-72.
- Walton B. Effects of anaesthesia and surgery on immune status. *Br J Anaesth*. 1979;51(1):37-43.
- O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA, Rodrick ML. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Annals of Surgery*. 1995;222(4):482-92.
- Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, et al. Suppression of cellular immunity by surgical stress. *Surgery*. 2000;127(3):329-36.
- Weissman C. The metabolic response to stress: an overview and update. *Anesthesiology*. 1990;73(2):308-27.
- Besedovsky H, del Rey A, Sorkin E, Dinarello CA. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science*. 1986;233(4764):652-4.
- Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332(20):1351-62.
- Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. *J Anesth*. 2008;22(3):263-77.
- Desborough JP. The stress response to trauma and surgery. *BJA: British Journal of Anaesthesia*. 2000;85(1):109-17.
- El Azab SR, Rosseel PM, De Lange JJ, van Wijk EM, van Strik R, Scheffer GJ. Effect of VIMA with sevoflurane versus TIVA with propofol or midazolam-sufentanil on the cytokine response during CABG surgery. *Eur J Anaesthesiol*. 2002;19(4):276-82.
- Liu S, Wang B, Li S, Zhou Y, An L, Wang Y, et al. Immune cell populations decrease during craniotomy under general anesthesia. *Anesth Analg*. 2011;113(3):572-7.
- Chong ZZ, Li F, Maiese K. Oxidative stress in the brain: novel cellular targets that govern survival during neurodegenerative disease. *Prog Neurobiol*. 2005;75(3):207-46.
- Yuki K, Eckenhoff RG. Mechanisms of the Immunological Effects of Volatile Anesthetics: A Review. *Anesth Analg*. 2016;123(2):326-35.
- Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune Modulation by Volatile Anesthetics. *Anesthesiology*. 2016;125(2):399-411.
- Smith MA, Hibino M, Falcione BA, Eichinger KM, Patel R, Empey KM. Immunosuppressive aspects of analgesics and sedatives used in mechanically ventilated patients: an underappreciated risk factor for the development of ventilator-associated pneumonia in critically ill patients. *Ann Pharmacother*. 2014;48(1):77-85.
- Hsu BG, Yang FL, Lee RP, Peng TC, Chen HI. Effects of post-treatment with low-dose propofol on inflammatory responses to lipopolysaccharide-induced shock in conscious rats. *Clin Exp Pharmacol Physiol*. 2005;32(1-2):24-9.
- Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. *PLoS One*. 2013;8(1):e52887.
- Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, et al. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-alpha, IL-6, and IL-1beta. *Neurobiol Aging*. 2012;33(7):1364-78.
- Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X. Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: the influence of anesthetic technique, cerebral injury and systemic inflammation. *BMC Anesthesiology*. 2015;15:154.
- Baki ED, Aldemir M, Kokulu S, Koca HB, Ela Y, Sivaci RG, et al. Comparison of the effects of desflurane and propofol anesthesia on the inflammatory response and s100beta protein during coronary artery bypass grafting. *Inflammation*. 2013;36(6):1327-33.
- Margarit SC, Vasian HN, Balla E, Vesa S, Ionescu DC. The influence of total intravenous anaesthesia and isoflurane anaesthesia on plasma interleukin-6 and interleukin-10 concentrations after colorectal surgery for cancer: a randomised controlled trial. *Eur J Anaesthesiol*. 2014;31(12):678-84.
- Dinarello CA. Historical insights into cytokines. *Eur J Immunol*. 2007;37 Suppl 1:S34-45.
- Banisadr G, Rostene W, Kitabgi P, Parsadaniantz SM. Chemokines and brain functions. *Curr Drug Targets Inflamm Allergy*. 2005;4(3):387-99.
- Citerio G, Pesenti A, Latini R, Masson S, Barlera S, Gaspari F, et al. A multicentre, randomised, open-label, controlled trial evaluating equivalence of inhalational and intravenous anaesthesia during elective craniotomy. *Eur J Anaesthesiol*. 2012;29(8):371-9.
- Marik PE. Propofol: an immunomodulating agent. *Pharmacotherapy*. 2005;25(5 Pt 2):28s-33s.
- Ding Z, Zhang J, Xu J, Sheng G, Huang G. Propofol administration modulates AQP-4 expression and brain edema after traumatic brain injury. *Cell Biochem Biophys*. 2013;67(2):615-22.
- Markovic-Bozic J, Karpe B, Potocnik I, Jerin A, Vranic A, Novak-Jankovic V. Effect of propofol and sevoflurane on the inflammatory response of patients undergoing craniotomy. *BMC Anesthesiology*. 2016;16:18.
- Berger M, Ponnusamy V, Greene N, Cooter M, Nadler JW, Friedman A, et al. The Effect of Propofol vs. Isoflurane Anesthesia on

Postoperative Changes in Cerebrospinal Fluid Cytokine Levels: Results from a Randomized Trial. *Front Immunol.* 2017;8:1528.

29. Huang W, Tang Y, Li L. HMGB1, a potent proinflammatory cytokine in sepsis. *Cytokine.* 2010;51(2):119-26.

30. Chaochao Q, Lou G, Yang Y, Liu Y, Hu Y, Min Z, et al. Macrophage Inflammatory Protein-2 in High Mobility Group Box 1 Secretion of Macrophage Cells Exposed to Lipopolysaccharide. *Cell Physiol Biochem.* 2017;42(3):913-28.

31. Li J-t, Wang H, Li W, Wang L-f, Hou L-c, Mu J-l, et al. Anesthetic Isoflurane Posttreatment Attenuates Experimental Lung Injury by Inhibiting Inflammation and Apoptosis. *Mediators of Inflammation.* 2013;2013:16.

32. Plachinta RV, Hayes JK, Cerilli LA, Rich GF. Isoflurane pretreatment inhibits lipopolysaccharide-induced inflammation in rats. *Anesthesiology.* 2003;98(1):89-95.

33. Karabiyik L, Sardas S, Polat U, Kocaba SN, Karakaya AE. Comparison of genotoxicity of sevoflurane and isoflurane in human lymphocytes studied in vivo using the comet assay. *Mutat Res.* 2001;492(1-2):99-107.

34. Crozier TA, Muller JE, Quittkat D, Sydow M, Wuttke W, Kettler D. Effect of anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth.* 1994;72(3):280-5.

35. Ke JJ, Zhan J, Feng XB, Wu Y, Rao Y, Wang YL. A comparison of the effect of total intravenous anaesthesia with propofol and remifentanyl and inhalational anaesthesia with isoflurane on the release of pro- and anti-inflammatory cytokines in patients undergoing open cholecystectomy. *Anaesth Intensive Care.* 2008;36(1):74-8.

36. Braz MG, Mazoti MA, Giacobino J, Braz LG, Golim Mde A, Ferrasi AC, et al. Genotoxicity, cytotoxicity and gene expression in patients undergoing elective surgery under isoflurane anaesthesia. *Mutagenesis.* 2011;26(3):415-20.

37. Braz MG, Braz LG, Braz JR, Pierine DT, Correa CR, Ferreira AL, et al. Comparison of oxidative stress in ASA physical status I patients scheduled for minimally invasive surgery under balanced or intravenous anesthesia. *Minerva Anesthesiol.* 2013;79(9):1030-8.

38. Orosz JE, Braz MG, Golim MA, Barreira MA, Fecchio D, Braz LG, et al. Cytokine profile in patients undergoing minimally invasive surgery with balanced anesthesia. *Inflammation.* 2012;35(6):1807-13.

39. El Beheiry H. Protecting the brain during neurosurgical procedures: strategies that can work. *Curr Opin Anaesthesiol.* 2012;25(5):548-55.