SEVOFLURANE VERSUS PROPOFOL ANESTHESIA ON EARLY POSTOPERATIVE COGNITIVE FUNCTION IN OLDER ADULTS: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Postoperative cognitive dysfunction (POCD) is a common complication after surgery. The present study compared the effects of sevoflurane and propofol on POCD in old patients undergoing laparoscopic surgery under general anesthesia.

Methods: Sixty patients over 65-year-old candidates for elective laparotomy were randomly assigned into two groups of anesthesia with sevoflurane or propofol. Baseline assessment of cognitive function was done 12-24 hours before surgery and the second to fourth tests were done at 6-12, 18-24, and 42-48 hours after surgery, respectively.

Results: The mean age, gender and the mean time of surgery were equal in two groups. Postoperative cognitive function in sevoflurane group was significantly better than propofol group in the 6-12 ($p<0.03$) and 12-24 ($p<0.03$) hours after surgery but the assessment of the two groups in 24-48 hours after surgery showed similar conditions.

Discussion: The results of this study showed that anesthesia with sevoflurane creates less cognitive disorders than anesthesia with propofol in patients without cerebrovascular complications or surgical procedures that involve the brain's blood flow.

Keywords: Postoperative cognitive dysfunction, sevoflurane, propofol

Introduction

Postoperative cognitive dysfunction (POCD) is a common complication after surgery. The disorder is reported in 9.1% to 17% of patients undergoing non-cardiac surgery on day 7 after surgery[1]. POCD is characterized by personality changes, cognitive dysfunction, or impaired memory and concentration after surgery[2]. The cognitive changes can occur both in short- and long-term. Some patients might experience short-term cognitive impairment (days to months), while others may have long-term cognitive changes (more than 6 months)[3]. Age is the main risk factor for POCD, which is clearly more prevalent among older adults[4]. Although the exact cause of POCD is still unknown, POCD risk factors are classified as related to age, comorbidities, surgery, and anesthesia. Urology, orthopedic and cardiovascular surgeries are associated with a higher risk[5]. Duration of surgery, the second surgery, postoperative infection, pulmonary complications, and acute postoperative pain are POCD risk factors in the first week after operation[5]. Alcohol

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use in older people is a POCD risk factors that affects visuospatial abilities and executive function[5]. Medications such as propofol, sevoflurane, nitrous oxide gas (N2O), midazolam and fentanil can lead to POCD by affecting different types of receptors in the brain[6]. Propofol and sevoflurane are commonly used during general anesthesia, and their effect on POCD is a concern among researchers. The present study compared the effects of sevoflurane and propofol on POCD in patients undergoing laparoscopic surgery under general anesthesia.

Methods

The present prospective, double-blind, randomized study recruited 60 over 65-year-old candidates of elective laparotomy surgery with American Society of Anesthesiologists (ASA) Class 1, 2, 3, in Shahid Beheshti Hospital of Kashan University of Medical sciences, Iran. After approval by the University Ethics Committee and obtaining informed consents, patients were randomly assigned into two groups of anesthesia with sevoflurane or propofol using a random number table. The patients and physicians who completed the questionnaires were not aware of the type of anesthesia. Patients with mini mental state examination (MMSE) score <23, inadequate education to complete the neuropsychological test, severe visual and hearing impairment, a history of known psychological disorders, consumption of antipsychotic, anti-anxiety and anti-depression medications, consumption of alcohol, a history of mental illness, addictions, sensitivity to anesthetic medications or unwillingness to cooperate in the study were excluded.

After admission to the operating room, intravenous access was established for patients and 10 ml/kg Ringer's solution was infused under standard monitoring including pulse oximetry, ECG with three leads, Non-invasive blood pressure (NIBP), (heart rate) HR, pulse oximetry (SpO2) Bispectral index (BIS), and (end-tidal carbon dioxide) ETCO2. Patients in both groups were pre-oxygenated for 3 minutes with 100% oxygen and received 2 mg/kg fentanil for premedication, after 5 minuts anesthesia was induced with 5 mg/kg intravenous sodium thiopental, and 0.5 mg/kg atracurium was used and trachea was intubated with an appropriate sized cuffed endotracheal tube. After verifying intubation by auscultation of chest and capnography, the patients were mechanically ventilated to maintain the ETCO2 between 4.7 kPa and 5.5 kPa. Propofol infusion at 150 μg/kg/min was used to maintain anesthesia in the propofol group. In the sevoflurane group, anesthesia was maintained with sevoflurane 1 Minimum alveolar concentration (MAC) in oxygen 30%. Atracurium (0.2 mg/kg/h) and fentanyl (2 μg/kg/h) were used for intraoperative relaxation and analgesia. Anesthesia was maintained at a BIS level of 40–60 by adjustment of flow of propofol or minimum alveolar concentration of sevoflurane. At the end of surgery, after reverse relaxation and ensuring the patient's normal respiratory status, they were transferred to the recovery room. The Visual Analogue Scale (VAS) was used to measure pain. Sodium diclofenac suppository was used and repeated every 6 hours for post-operative pain relief. In the case of pain in patients with VAS scores over 4, paracetamol infusion was administered for analgesia.

Patients' cognitive function measurement was performed using Mini-Mental State Examination (MMSE) in four steps. The first test was done 12-24 hours before surgery and the second to fourth tests were done at 6-12, 18-24, and 42-48 hours after surgery, respectively. MMSE was completed by a trained person and in a quiet room. This study was registered with the Iranian Registry of Clinical Trials (IRCT) number IRCT2012102211209N1.

Assessment of perioperative cognitive function

The present study used MMSE to identify POCD. This is the most common test used to assess postoperative cognitive function[1]. It is also known as the most suitable tool to monitor cognitive function in older adults in the United States, Canada, and the United Kingdom. Its wide applications provide the ability to compare the results of different studies[3]. MMSE evaluates the following[2]: Orientation (in time and place), memory (immediate and short-term), calculation, language (naming, repetition, listening and reading comprehension, writing), visual spatial awareness, concentration, and attention.

Data analysis and statistical analysis

Patients with a 20% decrease in cognitive function compared with the preoperative considered to be suffering from POCD. Data were analysed using SPSS software version 19. The categorical data were analysed by Fisher's exact test. The quantitative data were analysed using one-way analysis of variances (ANOVA). P<0.05 was considered to be statistically significant.

Sample size

In order to achieve the desired difference in the MMSE score of the two groups (d=1.5) with a power = 80% and type I error of 5%, the sample size was calculated as 30 subjects for each group.

Results

A total of 60 patients were included in two groups of propofol and sevoflurane. The mean age in the propofol and sevoflurane groups was 73±3.23 and 71±2.58, respectively (P=0.09). There were 17 (56.7%) males and 13 (43.3%) females in the propofol group and 15 (50%) males and 15 (50%) females in the sevoflurane group (P=0.605). The mean length of surgery was 72±12.15 in the propofol group and 75±15.2 in the sevoflurane group (P = 0.1).

Repeated measurement analysis was used to compare preoperative and postoperative cognitive function of patients in the two groups in several times. The confounding effects of primary scores of cognitive function in MMSE scale and gender were controlled in this analysis (p<0.001 and p=0.519, respectively). There is no interaction between the grouping factor and time (p=0.120), and then analysis showed that cognitive function in the sevoflurane group was significantly better than that in the propofol group (P=0.018).

The effect of time was not significant in this study (p=0.324). In other words, the result obtained at different times of the study had no significant difference.

The mean preoperative cognitive function score in the two groups was not statistically different. However, the groups had a significant difference in the 6-12 and 12-24 hours after surgery, where the sevoflurane group had better results. The assessment of the two groups in 24-48 hours after surgery showed similar conditions (Table 1).

Discussion

Postoperative cognitive dysfunction is a serious complication that is especially observed in older adult patients with memory and cognitive function impairment, reduced concentration, and deterioration in emotional and social behaviors[7]. The pathogenesis of postoperative cognitive problems is unclear, and various factors are involved such as age, alcohol use and type of surgery[8]. There is a higher risk of this complication in general anesthesia[9]. Anesthetics can create these complications by modifying cell receptors, apoptosis, changes in cholinergic receptors and gene expression[7]. Long-term consequences of POCD are important. Postoperative neurologic-cognitive dysfunction can remain permanently and severely affect patients' quality of life. The risk of death in these patients was significantly higher at 3 months and one year after surgery than that in the control group[3].

Table 1

Comparison of preoperative and postoperative cognitive function scores in the two groups

POCD Group	Preoperative	6-12 hours after surgery	12-24 hours after surgery	24-48 hours after surgery
Propofol	27.2±2.37	25.27 ± 1.85	26.03 ± 2.63	27.2 ±2.09
Sevoflurane	27.33±1.92	26.4±2.06	27.33±1.86	27.57±1.63
P-Value	0.81	0.03	0.03	0.45

POCD: Postoperative cognitive dysfunction.

The present study examined the effects of sevoflurane and propofol on early postoperative cognitive function of 60 older adults. The results showed that the cognitive function in the sevoflurane group was significantly better than propofol group. Previous studies have reported contradicting results in this regard. Biedler et al. examined patients undergoing elective gynecology surgery and cognitive function recovery appeared faster in sevoflurane group than propofol[10]. Another study investigated patients that underwent on-pump cardiac surgery and found that that postoperative cognitive status in patients anesthetized by sevoflurane was better than the propofol group[11]. These results were consistent with the result of the present study, while some other studies obtained different results. A clinical trial examined 30 patients undergoing hysteroscopy and cystoscopy after general anesthesia and found a similar status in the two groups regarding POCD[12]. A study by Kalimeris et al. on 44 patients who underwent carotid endarterectomy observed that patients anesthetized with propofol had a better cognitive status compared to the sevoflurane group during the first 24 hours after the sutgery, which was attributed to the reduced brain damage due to the antioxidant effects of propofol[13]. In a study by Larsen et al. the cognitive recovery in the group receiving propofol-remifentanil was better than the sevoflurane group within the 90 minutes after surgery[14]. The differences in the duration of anesthesia, underlying diseases, supplementary medications, the time of cognitive tests, and using different tests to assess cognitive status have led to those different results. The results of a study by Biedler et al. cannot be invoked because a limited number of patients and short duration of anesthesia. The results observed in a study by Kalimeris are attributed to propofol mechanisms. Propofol is a phenol and a powerful antioxidant that has reduced brain damage and resulted in better behavioral patterns of animal models under ischemia-reperfusion studies[15,16]. Sevoflurane reduces neuronal activity and cerebral metabolism levels and protects the brain[17]. Sevoflurane causes cerebrovascular vasodilatation and is followed by increased intracranial pressure. If a part of brain's blood supply fails (as in carotid endarterectomy surgery due to clamping one of the carotid arteries), this vasodilatation decreases blood supply in the impaired part and creates ischemic damage[18]. Meanwhile, propofol does not affect the blood supply to the affected areas and creates a protective effect on the nervous system in such conditions due to its antioxidant properties. In the case of a partial, unilateral and asymptomatic blockage in arteries supplying the brain, sevoflurane will affect patients' cognitive status more than propofol. This could be the issue leading to the adverse effect of sevoflurane in a study by Larsen et al. In the absence of vascular disorders or ischemic condition in the brain (such as elective general surgery) sevoflurane with reduced brain metabolism and increased intracranial blood flow, help the protection of the nervous system more than propofol.

Conclusion

The results of this study showed that anesthesia with sevoflurane creates less cognitive disorders than anesthesia with propofol in patients without cerebrovascular complications or surgical procedures that involve the brain's blood flow.

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Conflict of interest

We declare that we have no conflict of Interest.

References

1. Guo JY, Fang JY, Xu SR, Wei M, Huang WQ: Effects of propofol versus sevoflurane on cerebral oxygenation and cognitive outcome in patients with impaired cerebral oxygenation. *Ther Clin Risk Manag*; 2016 Jan 18, 12:81-5.
2. 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 Anesthesiol*; 2015 Oct 23, 15:154.

   Hussain M, Berger M, Eckenhoff RG, Seitz DP: General 3. anesthetic and the risk of dementia in elderly patients: current insights. *Clin Interv Aging*; 2014 Sep 24, 9:1619-28. doi: 10.2147/CIA.S49680.
4. Monk TG, Weldon BC, Garvan CW, Dede DE, Van Der AA MT, Heilman KM, et al: Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*; 2008, 108(1):18-30.

   Kirtania J, Sarbapali D, Pal R, Karl S, Basu M, S, Mandal 5. Kundu KK, Sarkar U, Gupta SD: Impact of general versus epidural anesthesia on early post-operative cognitive dysfunction following hip and knee surgery. *J Emerg Trauma Shock*; 2011, 4(1):23-28.
6. Goswami U, Babbar S, Tiwari S: Comparative evaluation of the effects of propofol and sevoflurane on cognitive function and memory in patients undergoing laparoscopic cholecystectomy: A randomized prospective study. *Indian J Anaesth*; 2015 Mar, 59(3):150-155.
7. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW: Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. *Br J Pharmacol*; 2005, 146:189-97.
8. Chen X, Zhao M, White PF, Li S, Tang J, Wender RH, Sloninsky A, Naruse R, Kariger R, Webb T, Norel E: The recovery of cognitive function after general anesthesia in elderly patients: a comparison of desflurane and sevoflurane. *Anesth Analg*; 2001 Dec, 93(6):1489-94, table of contents.
9. Mason SE, Noel-Storr A, Ritchie CW: The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. *J Alzheimers Dis*; 2010, 22:67-79.
10. Biedler A, Juckenhöfel S, Feisel C, Wilhelm W, Larsen R: [Cognitive impairment in the early postoperative period after remifentanil-propofol and sevoflurane-fentanyl anesthesia]. *Anaesthesist*; 2000, 49(4):286-90.
11. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger KU, et al: Cognitive function after sevoflurane-vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *Br J Anaesth*; 2011, 106(6):840-50.
12. Rohan D, Buggy DJ, Crowley S, Ling FK, Gallagher H, Regan C, Moriarty DC: Increased incidence of postoperative cognitive dysfunction 24hr after minor surgery in the elderly. *Can J Anaesth*; 2005, 52(2):137-42.
13. Kalimeris K, Kouni S, Kostopanagiotou G, Nomikos T, Fragopoulou E, Kakisis J, Vasdekis S, Matsota P, Pandazi A: Cognitive function and oxidative stress after carotid endarterectomy: comparison of propofol to sevoflurane anesthesia. *J Cardiothorac Vasc Anesth*; 2013, 27(6):1246-52.
14. Larsen B, Seitz A, Larsen R: Recovery of cognitive function after remifentanil-propofol anesthesia: a comparison with desflurane and sevoflurane anesthesia. *Anesth Analg*; 2000, 90(1):168-74.
15. Xi HJ, Zhang TH, Tao T, Song CY, Lu SJ, Cui XG, Yue ZY: Propofol improved neurobehavioral outcome of cerebral ischemia-reperfusion rats by regulating Bcl-2 and Bax expression. *Brain Res*; 2011, 1410:24-32.
16. Zheng YY, Lan YP, Tang HF, Zhu SM: Propofol pretreatment attenuates aquaporin-4 over-expression and alleviates cerebral edema after transient focal brain ischemia reperfusion in rats. *Anesth Analg*; 2008, 107(6):2009-16.
17. Eberspächer E, Eckel B, Engelhard K, Müller K, Hoffman WE, Blobner M, Werner C: Effects of sevoflurane on cognitive deficit, motor function, and histopathology after cerebral ischemia in rats. *Acta Anaesthesiol Scand*; 2009, 53(6):774-82.
18. McCulloch TJ, Thompson CL, Turner MJ: A randomized crossover comparison of the effects of propofol and sevoflurane on cerebral hemodynamics during carotid endarterectomy. *Anesthesiology*; 2007, 106(1):56-64.