European Review for Medical and Pharmacological Sciences 2019; 23: 849-856

Effect of propofol and sevoflurane anesthesia on postoperative cognitive function and levels of Aβ-42 and Tau in patients undergoing hepatectomy

J.-F. HOU, C.-L. XIAO

Department of Anesthesiology, Jiangxi Provincial People's Hospital, Nanchang, P.R. China.

Abstract. – OBJECTIVE: To investigate the effect of propofol and sevoflurane anesthesia on postoperative cognitive function.

PATIENTS AND METHODS: Medical records of 280 patients who underwent hepatectomy in Jiangxi Provincial People's Hospital from April 2012 to July 2016 were retrospectively analyzed. Among those patients, 135 patients underwent propofol anesthesia (propofol group), and 145 patients under sevoflurane combined anesthesia (sevoflurane group). Hemodynamics was recorded 5 min before the induction of anesthesia (T0), after the induction of anesthesia (T1), at the beginning of the incision (T2), immediately after the incision (T3) and after the end of the surgery (T4). According to the Mini-Mental State Examination (MMSE), patients' cognitive function was evaluated before surgery. The levels of Aβ-42 and Tau proteins in the patient's serum were measured.

RESULTS: The stability of the mean arterial pressure after induction of anesthesia in the propofol group was higher than that of the sevoflurane group ($p<0.05$). MMSE scores in the propofol group were higher than those in the sevoflurane group ($p<0.05$). MMSE scores of patients in both groups 7 days after surgery were higher than those at 3 days after surgery ($p<0.05$). At 3 and 7 days after surgery, the levels of Aβ-42 in the propofol group were lower than those in the sevoflurane group ($p<0.05$) and the levels of Tau protein in the propofol group were higher than those in the sevoflurane group. The levels of Aβ-42 and Tau protein on the 3rd day after surgery in both groups were significantly higher than those before surgery ($p<0.05$). The Aβ-42 levels decreased at 7 days after surgery in both groups ($p<0.05$). The level of Tau protein on the 7th day after surgery was higher than that before surgery and 3 days after operation ($p<0.05$).

CONCLUSIONS: Compared with sevoflurane anesthesia, propofol may improve postoperative Aβ-42 and Tau protein levels in patients with hepatocellular carcinoma, and ameliorate postoperative cognitive function.

Key Words:
Propofol, Sevoflurane, Hepatectomy, Cognitive function, Aβ-42, Tau protein.

Introduction

The incidence of liver cancer in developing countries is higher than that in developed countries; it is only lower than that of gastric cancer and esophageal cancer[1]. This disease affects people of all ages, especially the ones who are 40 to 49 years old[2]. The incidence of liver cancer in the male is higher than that in the female, and 6/7 liver cancer patients are male. Patients in China accounts for 42%, and the incidence in this country shows an increasing trend. This disease in China causes 600,000 new cases and 200,000 deaths each year[3,4].

Surgical treatment is the main treatment for liver cancer. However, cognitive dysfunction after surgery has always been a problem clinicians are working on. It has been confirmed that anesthesia can cause cognitive impairment in the brain, which in turn delays recovery and increases the economic burden. Cognitive dysfunction in severe cases may even cause death[5,6]. Therefore, how to improve anesthetic method to reduce the occurrence of cognitive impairment in patients is a big problem. Propofol, the most widely used

Corresponding Author: Chunlian Xiao, MD; e-mail: 578688828@qq.com

intravenous anesthetic in surgical treatment, acts through the γ-aminobutyric acid (GABA) A receptor to achieve anti-oxidation and anti-inflammatory effects[7]. Sevoflurane is a new type of inhalation anesthetic with no upper respiratory irritant effects and low respiratory depression. It inhibits N-methyl-D-aspartate (NMDA) receptor and causes rapid postoperative wakefulness[8]. Aβ-42 and Tau proteins are two proteins that have been shown to be associated with cognitive function and brain damage and are elevated in the serum of patients with brain injury[9,10].

In this work, medical records of 280 patients who underwent hepatectomy in the Jiangxi Provincial People's Hospital were analyzed to discover the effects of propofol and sevoflurane anesthesia on cognitive function and levels of Aβ-42 and Tau proteins.

Patients and Methods

Patients

Medical records of 280 patients who underwent hepatectomy in the Department of Oncology of Jiangxi Provincial People's Hospital from April 2012 to July 2016 were retrospectively analyzed. The age of those patients ranged from 19 to 68 years. Among those patients, 135 patients underwent propofol anesthesia (the propofol group), and 145 patients underwent sevoflurane combined anesthesia (the sevoflurane group). All patients were diagnosed with hepatocellular carcinoma by pathological examination in the Jiangxi Provincial People's Hospital with ASA grade of II-III. Hepatocellular carcinoma patients with abnormal leukocyte and lymphocyte counts were excluded. No distant metastasis was found based on imaging diagnosis and all patients were suitable for radical surgical resection. Patients did not receive any anti-tumor therapy before surgery, and had no history of other tumors, as well as cardiac or renal dysfunction. No abnormal bleeding or abnormal blood coagulation occurred before surgery. All patients had no allergies to propofol or sevoflurane. All patients had no history of alcohol abuse and use of nitroglycerin. Patients with Mini-Mental State Examination (MMSE) score<24 points before surgery, patients with incomplete clinical data, or with a history of hepatitis, with mental or learning disabilities, and patients with large tumor diameters were excluded. This study was approved by the Ethics Committee of the Jiangxi Provincial People's Hospital and patients or their families signed an informed consent.

Anesthetic Method

All patients fasted for 8 hours before the surgery, and preoperative drug use was forbidden. Intravenous injection of midazolam (0.2 mg/kg, Jiangsu Enhua Pharmaceutical Group Co., Ltd., Jiangsu, China) was performed 20 min before surgery. Invasive arterial pressure, central venous pressure, electrocardiogram, blood pressure, heart rate, pulse and oxygen protection monitoring were established. In the propofol group, propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China) was used for target-controlled infusion (plasma concentration 3 μg/ml), and intravenous injection of fentanyl (Yichang Renfu Pharmaceutical Co., Ltd., Hubei, China) at a dose of 3 μg/kg and atracurium (Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China) at a dose of 0.3 mg/kg was performed for rapid induction of endotracheal intubation. After intubation, oxygen flow was 2.0 L/min after intubation, tidal volume was 8-10 ml/kg, respiratory rate was 10-12 beats/min and inhalation ratio was 1:1.5. Anesthesia was maintained with a Target Controlled Infusion (TCI) pump (cp-660tci pump, Shanghai Yuxing Medical Devices Co., Ltd., Shanghai, China) targeted infusion of propofol to maintain a plasma concentration of 4 μg/ml. In the sevoflurane group, 6% sevoflurane (Fujian Gutian Pharmaceutical Co., Ltd., Fujian, China) inhalation was initially performed using 5 L/min oxygen flow. Patients were asked to take a deep breath. After consciousness disappeared, positive pressure manual ventilation was performed, the oxygen flow was reduced to 2 L/min, and the sevoflurane concentration in the volatilization tank is adjusted so that the concentration of the end-tidal sevoflurane is maintained at 1.0 minimum alveolar concentration (MAC). Intravenous injection of fentanyl at a dose of 3 μg/kg and atracurium at a dose of 0.5-0.6 mg/kg was performed to rapidly induce endotracheal intubation. Continuous inhalation of 3% sevoflurane was performed to maintain anesthesia. Patients in both groups were continuously infused with atracurium and fentanyl with a microinfusion pump to maintain bispectral index (BIS) at 40 to 60%.

Observation Indicators

Hemodynamics was recorded 5 min before the induction of anesthesia (T0), after the induction of anesthesia (T1), at the beginning of the incision

(T2), immediately after the incision (T3) and after the end of the surgery (T4). According to MMSE, patients' cognitive function was evaluated preoperatively, 3 days after the operation (3 days), and 7 days after the operation (7 days). The levels of Aβ-42 and Tau proteins in the patients' serum were measured by ELISA using kits provided by Life Technologies (Waltham, MA, USA).

Statistical Analysis

SPSS19.0 (SPSS Inc., Chicago, IL, USA) was used. Count data were recorded as [n(%)] and compared using the χ^2-test. Measurement data were expressed as $\bar{x}$±sd, and *t*-test was used for comparisons between the two groups. Repeated-measures analysis of variance was used for comparisons among different times within the same group. $p<0.05$ was considered to be statistically significant.

Results

General Information

280 patients were included in this study. Patients in the propofol group (n=135) included 105 males and 30 females, with an average age of (50.9±6.1) years. Patients in the sevoflurane group (n=145) included 109 males and 36 females, with a mean age of (49.7±5.7) years. There was no difference in gender and age between the two groups ($p>0.05$). No significant differences in other basic data such as operative time, time of recovery, ASA classification ratio, tumor differentiation and educational level were found between the two groups ($p>0.05$) (Table I).

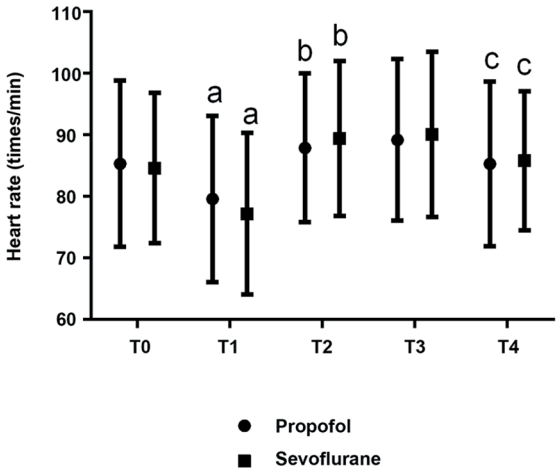

Figure 1. Heart rate changes in both groups. There was no significant difference between the two groups in heart rate at five time points ($p>0.05$). At T1, heart rate of both groups was significantly lower than that at T0 ($p<0.05$). At T2, heart rate of both groups was higher than that at T1 ($p<0.05$), and there was no difference when compared with T0 ($p>0.05$). At T3, heart rate of both groups was similar to that at T2, and there was no difference compared with T2 ($p>0.05$), but it was increased compared with T0 and T1 ($p<0.05$). At T4, heart rate decreased in the two groups of patients compared with T0, T1, T2 and T3. Notes: a, compared with T0, $p<0.05$; b, compared with T1, $p<0.05$, c, compared with T3, $p<0.05$.

Perioperative Hemodynamic Analysis

There was no significant difference in heart rate between the two groups at 5-time points ($p>0.05$).

Table I. Comparison of general data between two groups of patients.

	Propofol group (n=135)	Sevoflurane group (n=145)	χ^2	*p*
Gender			0.263	0.608
Male	105	109		
Female	30	36		
(age)	50.9±6.1	49.7±5.7	1.702	0.090
Operation time (min)	194.5±42.4	196.8±45.6	0.436	0.663
Wake-up time (min)	22.1±8.2	23.3±9.4	1.135	0.258
ASA (n%)]			0.861	0.353
II	68 (50.4)	65 (44.8)		
III	67 (49.6)	80 (55.2)		
Degree of differentiation [(n%)]			0.391	0.532
I, II	98 (72.6)	110 (75.9)		
III, IV	37 (27.4)	35 (24.1)		
Education level [(n%)]			0.170	0.680
Junior high school and below	87 (64.4)	90 (62.1)		
Junior high school	48 (35.6)	55 (37.9)		

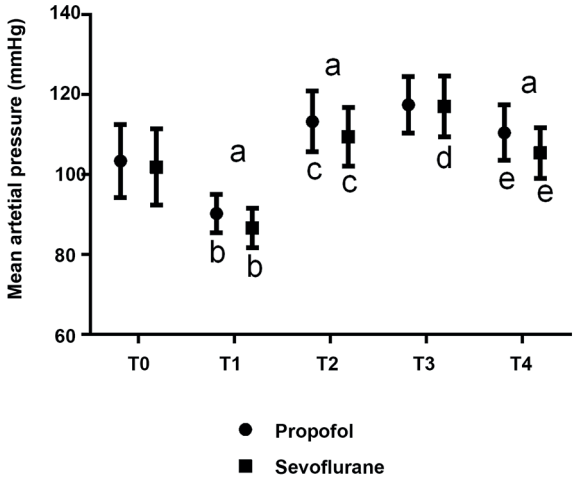

Figure 2. Changes in mean arterial pressure in two groups of patients. There was no significant difference in mean arterial pressure between the two groups at T0 and T3 (p>0.05). Mean arterial blood pressure was higher in the propofol group than in the sevoflurane group at T1, T2 and T4 (p<0.05). At T1, mean arterial pressure was significantly lower in the two groups compared with T0 (p<0.05). At T2, mean arterial pressure was significantly higher in the two groups compared with T1 (p<0.05), and there was no significant difference when compared with T0 (p>0.05). At T3, mean arterial pressure in propofol group showed no significant difference to that of T2 (p>0.05), but mean arterial pressure was significantly increased in the sevoflurane group compared with T2. At T4, mean arterial pressure decreased significantly in both groups compared with T0, T1, T2 and T3 (p<0.05). Notes: a, compared to propofol group, p<0.05; b, compared to T0, p<0.05; c, compared with T1, p<0.05; d, compared with T2, p<0.06; e, compared with T3, p<0.05.

Mean arterial pressure was significantly higher in the propofol group than in the sevoflurane group at T1, T2, and T4 (p<0.05). At T1, heart rate and mean arterial pressure of both groups were significantly lower than those at T0 (p<0.05). At T2, heart rate and mean arterial pressure were significantly higher in both groups than those at T1 (p<0.05), and there was no significant difference when compared with T0 (p>0.05). At T3, heart rate and mean arterial pressure in patients of the propofol group were similar to those at T2 (p>0.05), while heart rate and mean arterial pressure in the two groups were higher than those at T0 and T1 (p<0.05). At T4, heart rate and mean arterial pressure of both groups were significantly decreased when compared with T0, T1, T2, and T3. (p<0.05) (Figures 1, 2).

Cognitive Function Assessment of the Two Groups

There was no significant difference in preoperative MMSE scores between the two groups (p>0.05). There was a statistically significant difference in MMSE between the two groups on 3 and 7 days after operation (p<0.05), and MMSE scores in the propofol group were higher than those in the sevoflurane group. MMSE scores of the two groups were lower on the 3rd day after operation than those before surgery (p<0.05). MMSE scores of patients in the propofol group returned to pre-operation level on the 7th day after surgery (p>0.05), and were higher than those on the 3rd after surgery (p<0.05). MMSE scores in the sevoflurane group on the 7th day after surgery were higher than those on the 3rd after surgery, but were still lower than preoperative MMSE scores (p<0.05) (Figure 3).

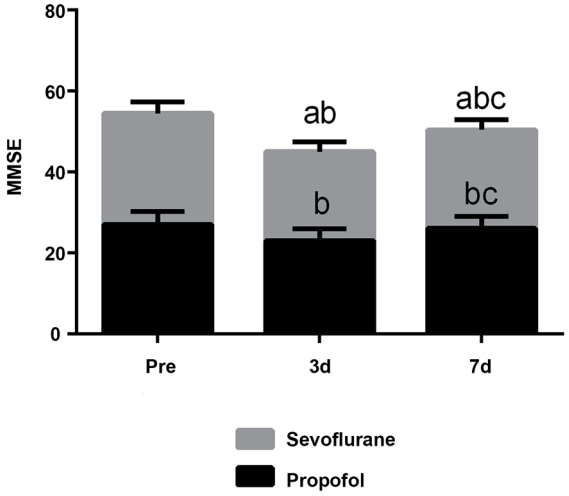

Figure 3. Assessment of cognitive function in both groups. No significant difference in preoperative MMSE scores was found between the two groups (p>0.05). There was a statistically significant difference in MMSE between the two groups on 3 days and 7 days after operation (p<0.05), and MMSE scores in the propofol group were higher than those in the sevoflurane group. MMSE scores of the two groups were lower on 3rd day after operation than those before surgery (p<0.05). MMSE scores of patients in the propofol group returned to the pre-operation level on 7th day after surgery (p>0.05), and were higher than those on 3rd after surgery (p<0.05). MMSE scores in the sevoflurane group on the 7th day after surgery were higher than those on the 3rd after surgery, but were still lower than preoperative MMSE scores (p<0.05). Notes: a, compared with the propofol group, p<0.05; b, compared with the preoperative level, p<0.05; c, compared with the level at 3rd day after surgery, p<0.05.

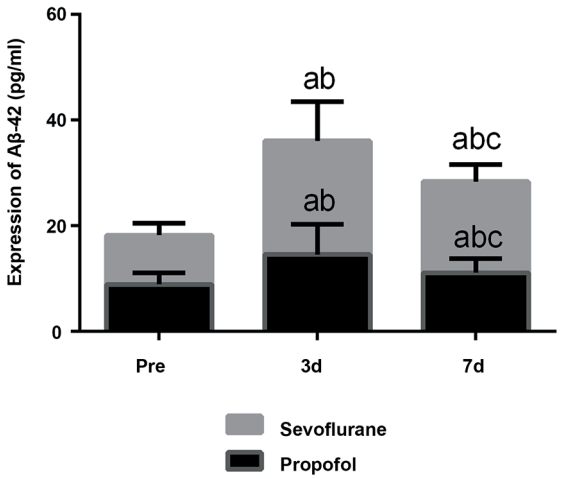

Figure 4. Aβ-42 test results in the two groups. There was no difference in the level of preoperative Aβ-42 protein level between the two groups (p>0.05). At 3 days and 7 days after operation, the level of Aβ-42 in the propofol group was lower than that in the sevoflurane group (p<0.05). The level of Aβ-42 protein in both groups on the 3rd day after operation was higher than that before surgery (p<0.05). Aβ-42 level was decreased at 7 days postoperatively in both groups compared with 3rd day after the operation (p<0.05), but it was still higher than the preoperative level (p<0.05). Notes: a, compared with the propofol group, p<0.05; b, compared with the preoperative level, p<0.05; c, compared with 3 days after operation, p<0.05.

Aβ-42 and Tau Protein Levels in the Two Groups

There was no difference in the preoperative levels of Aβ-42 and Tau protein between the two groups (p>0.05). At 3 and 7 days after surgery, the levels of Aβ-42 in the propofol group were lower than those in the sevoflurane group (p<0.05) and the levels of Tau protein in the propofol group were higher than that in the sevoflurane group. The levels of Aβ-42 and Tau protein on the 3rd day after surgery in both groups were significantly higher than those before surgery (p<0.05). The Aβ-42 level was decreased at 7 days postoperatively in both groups (p<0.05), but it was still higher than the preoperative level (p<0.05). The level of Tau protein on the 7th day after surgery was higher than that before surgery and 3 days after surgery (p<0.05) (Figures 4 and 5).

Discussion

At present, the effects of propofol and sevoflurane on cognitive function after anesthesia have been extensively reported. Goswami et al[11] reported that sevoflurane anesthesia had less influence on cognitive function in patients undergoing cholecystectomy than propofol. Tian et al[12] reported that propofol had less effect on cognitive function in patients undergoing lung cancer resection than sevoflurane. The effects of propofol and sevoflurane anesthesia on cognitive function of patients in distinct operations are different, but the effects of propofol and sevoflurane on cognitive function of patients undergoing hepatectomy are still not well studied. Aβ42 has been shown to induce apoptosis and is closely associated with the risk of cognitive impairment in patients[13]. Tau protein is the most abundant microtubule-structure-associated protein in nerve cells and has also been shown to be associated with cognitive dysfunction. In this study, we analyzed the medical records of patients who underwent hepatocellular carcinoma resection and investigated the effects of propofol or sevoflurane anesthesia on cognitive function and levels of Aβ-42 and Tau.

The results of this study showed no difference in heart rate and mean arterial pressure between the two groups before surgery, but the stability of mean arterial pressure after induction of anesthesia

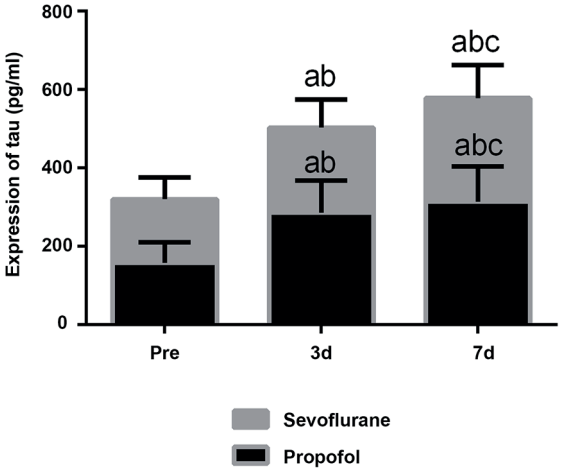

Figure 5. Tau test results in the two groups. There was no difference in the level of preoperative Tau protein level between the two groups (p>0.05). At 3 days and 7 days after operation, the level of Tau in the propofol group was lower than that in the sevoflurane group (p<0.05). The level of Tau protein in both groups on the 3rd day after the operation was higher than that before surgery (p<0.05). Tau protein level in both groups on the 3rd day after the operation was higher than the preoperative level (p<0.05). The level of Tau protein in the two groups on the 7th day after operation was higher than that before surgery and 3 days after surgery (p<0.05). Notes: a, compared with the propofol group, p<0.05; b, compared with the preoperative level, p<0.05; c, compared with 3 days after operation, p<0.05.

was higher in the propofol group than that in the sevoflurane group, indicating that propofol was more effective than sevoflurane in maintaining hemodynamic stability in liver cancer patients after anaesthesia induction during hepatectomy. However, there are also reports on that sevoflurane is superior to propofol in maintaining hemodynamic stability in patients undergoing surgery[14]. This may be due to the different subjects in our work. For patients undergoing cholecystectomy, studies found that liver cancer resection has a greater impact on liver function; propofol is mainly metabolized by the liver, and sevoflurane is excreted via respiration[15,16]. It is possible that the ability of propofol and sevoflurane to maintain hemodynamic stability in patients is related to the degree of liver function. However, in recent years, there have been only a few reports on the effect of liver function on the maintenance of hemodynamic stability by propofol and sevoflurane, so this hypothesis still needs to be verified. In this study, the MMSE score table was used to assess patients' cognitive function. MMSE is a scale that is commonly used to assess cognitive function. It is easy to operate and has high efficiency and feasibility. It can reduce the effects of the patients' mood as well as abnormal consciousness on the assessment of cognitive function[17,18]. The analysis of the cognitive function of patients in the two groups in this study showed that it experienced fluctuations in different degrees on the 3rd day after surgery, but the decrease in the MMSE score was lower in the propofol group than in the sevoflurane group. At 7 days after surgery, cognitive function in the propofol group returned to a similar level before surgery, but cognitive function in the sevoflurane group was still lower than that before surgery. Based on those data, we can speculate that the effect of propofol on the postoperative cognitive function of patients undergoing liver cancer resection is lower than that of sevoflurane. Propofol is the most commonly used in intravenous anesthesia. By increasing the effect of GABA A receptors, it causes abnormal phosphorylation of multiple sites of Tau protein in the hippocampus of the brain, leading to an increase in its expression level, resulting in cognitive dysfunction[19,20]. Sevoflurane is a fluoride-containing anesthetic used in inhalation anesthesia. It inhibits the postsynaptic transmission of cholinergic neurons by inhibiting the action of NMDA receptors, but it also inhibits synaptic function for a long time, thus causing cognitive dysfunction[21,22]. To investigate why propofol and sevoflurane have different effects on the cognitive function of patients undergoing hepatocellular carcinoma resection, we analyzed the changes in Aβ-42 and Tau protein levels of patients in two groups. Aβ-42, the most toxic β-amyloid protein, is an important part of β-amyloid polymerization that mediates oxidative stress injury, inflammatory response, cholinergic nerve damage, changes in membrane ion channels and neuronal apoptosis[23,24]. Tau protein is a microtubule-associated protein with the highest expression level in neurons and a major protein component of neurofibrillary tangles, and is an important protein for maintaining the integrity of neuronal axons[25,26]. In this study, the results showed that the Aβ-42 and Tau protein levels increased on the 3rd day after surgery in both groups, but the Aβ-42 level in the propofol group was significantly lower than that in the sevoflurane group. Tau protein level was significantly higher in the propofol group than that in the sevoflurane group. On the 7th day after surgery, Aβ-42 levels in both groups decreased, but they were still higher than preoperative levels, while Tau protein level increased continuously, but in the propofol group Aβ-42 levels were significantly lower than those in the sevoflurane group, and Tau protein levels were significantly higher than those in the sevoflurane group. Many studies have also reported that postoperative Aβ-42 and Tau proteins are elevated in patients with liver cancer[27], which is consistent with our findings. Therefore, we speculate that the stimulation of traumatic surgery and anesthesia causes elevated Aβ-42 levels, promotes β-amyloid aggregation, induces neuronal cell apoptosis and exerts neurotoxic effects. This stimulation also leads to an elevated level of Tau protein. This may be a protective response of the body to injury stimuli to inhibit the apoptosis of neurons and protect nerve function. Different changes in these two protein levels cause different changes in cognitive function after liver cancer resection. However, due to limited resources, regulation of Aβ-42 and Tau levels by propofol and sevoflurane was not investigated. In addition, the sample size in this work is small. Further studies are still needed to further confirm our conclusions.

Conclusions

We found that, compared with sevoflurane anesthesia, propofol may improve postoperative Aβ-

42 and Tau protein levels in patients with hepatocellular carcinoma, and ameliorate postoperative cognitive function, which is worthy of clinical application.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer 2014; 3: 458-468.
2) Kudo M. Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. Liver Cancer 2015; 4: 39-50.
3) Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74: 2913-2921.
4) Oishi N, Yamashita T, Kaneko S. Molecular biology of liver cancer stem cells. Liver Cancer 2014; 3: 71-84.
5) Polunina AG, Golukhova EZ, Guekht AB, Lefterova NP, Bokeria LA. Cognitive dysfunction after on-pump operations: neuropsychological characteristics and optimal core battery of tests. Stroke Res Treat 2014; 2014: 302824.
6) Shi HJ, Xue XH, Wang YL, Zhang WS, Wang ZS, Yu AL. Effects of different anesthesia methods on cognitive dysfunction after hip replacement operation in elder patients. Int J Clin Exp Med 2015; 8: 3883-3888.
7) Qiu Q, Choi SW, Wong SS, Irwin MG, Cheung CW. Effects of intra-operative maintenance of general anaesthesia with propofol on postoperative pain outcomes - a systematic review and meta-analysis. Anaesthesia 2016; 71: 1222-1233.
8) Lapebie FX, Kennel C, Magy L, Projetti F, Honnorat J, Pichon N, Vignon P, Francois B. Potential side effect of propofol and sevoflurane for anesthesia of anti-NMDA-R encephalitis. BMC Anesthesiol 2014; 14: 5.
9) Franz G, Beer R, Kampfl A, Engelhardt K, Schmutzhard E, Ulmer H, Deisenhammer F. Amyloid beta 1-42 and tau in cerebrospinal fluid after severe traumatic brain injury. Neurology 2003; 60: 1457-1461.
10) Rylott EL, Rogers CA, Gilday AD, Edgell T, Larson TR, Graham IA. Arabidopsis mutants in short- and medium-chain acyl-CoA oxidase activities accumulate acyl-CoAs and reveal that fatty acid beta-oxidation is essential for embryo development. J Biol Chem 2003; 278: 21370-21377.
11) 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 randomised prospective study. Indian J Anaesth 2015; 59: 150-155.
12) Tian HT, Duan XH, Yang YF, Wang Y, Bai QL, Zhang X. Effects of propofol or sevoflurane anesthesia on the perioperative inflammatory response, pulmonary function and cognitive function in patients receiving lung cancer resection. Eur Rev Med Pharmacol Sci 2017; 21: 5515-5522.
13) Mattsson N, Lonneborg A, Boccardi M, Blennow K, Hansson O. Clinical validity of cerebrospinal fluid Abeta42, tau, and phospho-tau as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework. Neurobiol Aging 2017; 52: 196-213.
14) Bonhomme V, Demoitie J, Schaub I, Hans P. Acid-base status and hemodynamic stability during propofol and sevoflurane-based anesthesia in patients undergoing uncomplicated intracranial surgery. J Neurosurg Anesthesiol 2009; 21: 112-119.
15) Lian QQ, Pan PP, Li JW, Lin H, Hu GX, Zuo MZ, Cai JP. Impact of CYP2C9 polymorphism found in the Chinese population on the metabolism of propofol in vitro. Biol Pharm Bull 2015; 38: 531-535.
16) Natalini CC, Da Silva Serpa PB, Cavalcanti RL, Polydoro AS, Griffith JE, Santos LC, Nicholson A. General anesthesia with an injectable 8% v/v sevoflurane lipid emulsion administered intravenously to dogs. Vet Anaesth Analg 2016; 43: 271-280.
17) Wee LE, Yeo WX, Yang GR, Hannan N, Lim K, Chua C, Tan MY, Fong N, Yeap A, Chen L, Koh GC, Shen HM. Individual and area level socioeconomic status and its association with cognitive function and cognitive impairment (low MMSE) among community-dwelling elderly in Singapore. Dement Geriatr Cogn Dis Extra 2012; 2: 529-542.
18) Mai LM, Sposato LA, Rothwell PM, Hachinski V, Pendlebury ST. A comparison between the MoCA and the MMSE visuoexecutive sub-tests in detecting abnormalities in TIA/stroke patients. Int J Stroke 2016; 11: 420-424.
19) Levenga J, Krishnamurthy P, Rajamohamedsait H, Wong H, Franke TF, Cain P, Sigurdsson EM, Hoeffer CA. Tau pathology induces loss of GABAergic interneurons leading to altered synaptic plasticity and behavioral impairments. Acta Neuropathol Commun 2013; 1: 34.
20) Haddock JH, Mercante DE, Paccione R, Breaux JL, Jolley SE, Johnson JL, Connolly SE, deBoisblanc BP. Use of digital pupillometry to measure sedative response to propofol. Ochsner J 2017; 17: 250-253.
21) Charlesworth M, Ashworth A, Stirling S. Isoflurane use is not associated with prolonged intensive care unit stay following routine cardiac surgery when compared to sevoflurane. Can J Anaesth 2017; 64: 100-101.

22) Bellanti F, Mirabella L, Mitarotonda D, Blonda M, Tamborra R, Cinnella G, Fersini A, Ambrosi A, Dambrosio M, Vendemiale G, Serviddio G. Propofol but not sevoflurane prevents mitochondrial dysfunction and oxidative stress by limiting HIF-1alpha activation in hepatic ischemia/reperfusion injury. Free Radic Biol Med 2016; 96: 323-333.

23) Sekiya M, Wang M, Fujisaki N, Sakakibara Y, Quan X, Ehrlich ME, De Jager PL, Bennett DA, Schadt EE, Gandy S, Ando K, Zhang B, Iijima KM. Integrated biology approach reveals molecular and pathological interactions among Alzheimer's Abeta42, Tau, TREM2, and TYROBP in Drosophila models. Genome Med 2018; 10: 26.

24) Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. Lancet Neurol 2017; 16: 66-75.

25) Nathan PJ, Lim YY, Abbott R, Galluzzi S, Marizzoni M, Babiloni C, Albani D, Bartres-Faz D, Didic M, Farotti L, Parnetti L, Salvadori N, Müller BW, Forloni G, Girtler N, Hensch T, Jovicich J, Leeuwis A, Marra C, Molinuevo JL, Nobili F, Pariente J, Payoux P, Ranjeva JP, Rolandi E, Rossini PM, Schönknecht P, Soricelli A, Tsolaki M, Visser PJ, Wiltfang J, Richardson JC, Bordet R, Blin O, Frisoni GB. Association between CSF biomarkers, hippocampal volume and cognitive function in patients with amnestic mild cognitive impairment (MCI). Neurobiol Aging 2017; 53: 1-10.

26) Schindler SE, Jasielec MS, Weng H, Hassenstab JJ, Grober E, McCue LM, Morris JC, Holtzman DM, Xiong C, Fagan AM. Neuropsychological measures that detect early impairment and decline in preclinical Alzheimer disease. Neurobiol Aging 2017; 56: 25-32.

27) Apostolova LG. Alzheimer disease: a quantitative trait approach to GWAS pays dividends. Nat Rev Neurol 2017; 13: 321-322.

.