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Comparative study on the effect of two different anesthesia methods on expression of peripheral blood inflammatory cytokines IL-1β and IL-17 in patients with surgery for liver cancer.

Quanjun Cao[1#], Ke Zhang[1#], Jing Li[2*]

[1]Department of Anesthesiology, People's Hospital of Linzi District, Shandong, Zibo, PR China

[2]Department of Anesthesiology, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, PR China

[#]These authors contributed equally.

Abstract

Objective: To investigate and compare the effect of two different anesthesia methods on expression of peripheral blood inflammatory cytokines IL-1β and IL-17 in patients with surgery for liver cancer.

Methods: 60 elderly patients with liver cancer that underwent radical resection from January 2014 to January 2016 were enrolled in this study. According to the different methods of anesthesia, patients were randomly divided into observation group (n=30) and control group (n=30). Observation group were given target controlled infusion of sufentanil combined with propofol while control group received continuous intravenous infusion of sufentanil and propofol target controlled infusion for anesthesia maintenance in surgery. The cognitive function reflected by Mini-mental State Examination (MMSE) scores. Oxidative stress was estimated through Malondialdehyde (MDA) levels and superoxide dismutase (SOD) levels, MDA levels were detected by the thiobarbituric acid method and SOD levels were detected by the xanthine oxidase method, expression levels of IL-1β, IL-17, amyloid beta proteins S100β and Aβ were compared between two groups before anesthesia, 1h after anesthesia and 1 day after operation.

Results: Cognitive function reflected by the MMSE scores in the two groups were both significantly decreased 1 hour after anesthesia (P<0.05). However, the scores of observation group were significantly higher than those of control group both 1h after anesthesia and 1 day after operation (P<0.05). There was no statistically significant difference in superoxide dismutase (SOD) activity and malondialdehyde (MDA) score before anesthesia between the two groups (P>0.05). However, MDA levels were increased and SOD activity was decreased 1h after anesthesia and 1 day after operation, and the range of change was relatively small in observation group (P<0.05). In observation group, the expression levels of IL-1β and IL-17 were significantly lower than those in control group 1h after anesthesia and 1 day after operation (P<0.05), but with no significant difference from those before anesthesia (P>0.05). While in control group there was significant difference in the expression levels of IL-1β and IL-17 between 1 h after anesthesia as well as 1d after operation and those before anesthesia (P<0.05). Compared with before anesthesia, the expression levels of amyloid beta proteins S100β and Aβ increased significantly 1h after anesthesia and 1d after operation in the two groups. However, the degree of increase in observation group was significantly lower than that in control group (P<0.05).

Conclusion: During radical resection for liver cancer, both two methods of anesthesia will affect patient's postoperative cognitive function to a certain extent, but sufentanil combined with propofol target controlled infusion has relatively smaller effect and better inhibits stress response in patients after anesthesia, thus serving as an ideal method of anesthesia and analgesia.

Keywords: Anesthesia, Sufentanil, Cognitive function, Stress.

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Introduction

Liver cancer is one of the most common malignant tumors in our country, which poses a serious threat to people's life safety and health [1,2]. At present, it is mainly treated in clinical practices by surgery, chemotherapy and radiotherapy, in which radical resection is the most effective treatment for early and medium-term liver cancer, which can remove primary tumors, metastatic lymph node as well as invasive tissues and provide the best prognosis for patients. The methods of anesthesia have

a closed relation to cancer [3]. In the clinic, Malondialdehyde (MDA) levels and superoxide dismutase (SOD) levels have often been treated as matching indicators, of which the SOD level was associated with free radical scavenging ability, whereas MDA reflected the degree of damage caused by free radicals to the cells [4]. The occurrence and development of liver cancer are associated with immune function, although the surgical treatment has significant effect in this regard, the inhibition of immune function induced by surgical stress can promote tumor cell growth and metastasis, it is suggested in clinical studies that the incidence of primary carcinoma of liver is closely related to change of microenvironment where IL-17 can facilitate growth and metastasis of tumors like fibrosarcoma, colon cancer and liver cancer. It can promote the formation of tumoral angiogenesis through aggregation of vascular endothelial cells and also facilitate fibroblast to generate vascular endothelial growth factor, prostaglandins as well as chemokines. And the generation of transforming growth factors promotes the adhesion and migration of tumor cells, which provides conditions for formation of tumor angiogenesis and dissemination of cancer cells; IL-1β is a lymphocyte activating factor (LAF) and takes secondary action in the development of inflammation, persistently high level of IL-1β can induce chronic inflammation and tissue destruction and is a factor resulting in tumorigenesis and deterioration of biological behavior.

Table 1. *Comparison of MMSE scale scores between the two groups ($\bar{x}$ ± s, score).*

Groups	Number	Before anesthesia	1 h after anesthesia	1 d after operation
observation group	30	30.03 ± 4.22	24.76 ± 3.20	27.12 ± 4.00
control group	30	29.86 ± 3.99	18.20 ± 3.11	23.46 ± 3.22
t		1.523	15.852	4.582
P		>0.05	<0.05	<0.05

These two inflammatory factors play an important role in reflecting the immune function of liver cancer patients. In addition, different anesthetic methods and drugs exert varying effects on the patients' immune function [5,6], and most studies show that [7,8] some patients are prone to inappropriate behaviors like groan, irritability, limb dysfunction and delirium after general anesthesia and it will also inhibit the immunity of patients, so during effective surgical treatment, the doctor also should adopt proper anesthetic drugs and operative types to help with successful operation and ensure smooth postoperative recovery in patients. Sufentanil and propofol are both powerful analgesic drugs and have high clinical value in thoracic surgical procedures. However, postoperative cognitive dysfunction is a common adverse effect of anesthesia which refers to the disorder of consciousness, cognition and memory after the operation and is frequently tested by MMSE in clinical practices. The changes of S100β level can reflect the severity as well as prognosis of brain injury and play a certain role in learning and memory process. Typically, when there is cell trauma in central nervous system or permeability of blood brain barrier is increased, S100β would seep from the cytosol into the cerebrospinal fluid and enter bloodstream through the damaged blood-brain barrier [9]. Aβ is a protein of senile dementia characteristics and is associated with cognitive impairment. But at present, which method is most appropriate remains controversial. The author respectively carried out sufentanil intravenous constant injection and sufentanil intravenous constant injection with propofol target controlled infusion in radical resection for liver cancer in elder patients so as to provide more references for anesthesia ways in clinical trials.

Data and Materials

General information

Sixty (60) elderly patients with liver cancer that underwent radical resection from January 2014 to January 2016 were enrolled in this study. Inclusion criterion: (1) all patients received surgical treatment at the first time; (2) all patients followed surgical indications; (3) all patients had no other diseases; (4) all patients and their families agreed to take part in the study and singed informed consent form and the study was approved by hospital ethics. Exclusion criteria: (1) patients with a history of allergy to anesthesia; (2) patients with cognitive impairment or past history of mental illness; (3) patients with long-term medication of opioid drug. Among 60 patients, there were 48 males and 12 females, with a mean age of (44.20 ± 4.11) years,39 cases with educational level above junior middle school and 21 cases with educational level below junior middle school, and the difference between the two groups in paired factors (age, education degree and pathological type) was not statistically significant (P>0.05).

Methods

According to the different methods of anesthesia, patients were randomly divided into observation group (n=30) and control group (n=30). All patients took no medication before operation and after entering the operating room their vital signs were monitored and venous puncture of upper limbs was done to establish venous access, anesthesia was induced by using atropine 0.3 mg, dexamethasone 5 mg, propofol 1.5 mg, sufentanil 0.5 μg/kg and atracurium 0.8 mg, double lumen tube was inserted followed by mechanical ventilation with respiratory rate set as 10-12 time/min and tidal volume 8-10 mL/kg. The observation group were treated by sufentanil combined with propofol target controlled infusion with the initial blood plasma target concentration of 1% 1 μg/ml propofol infusion, which was adjusted to 1% 0.5 μg/ml propofol infusion when the blood concentration reached a preset value, once there was loss of consciousness in patients, the target controlled infusion of 0.2 μg/kg sufentanil was immediately given. The control group were treated by intravenous sufentanil constant injection and propofol target controlled infusion with the initial blood plasma target concentration and the adjustment of blood concentration while

reaching a preset value same as those in the observation group, but with no additional injection of sufentanil. In the course of implementing anesthesia, vital signs like blood pressure and heart rate should be measured continuously in the two groups.

Observation index

The cognitive function reflected by Mini-mental State Examination (MMSE) scores. The MMSE consists of 30 items intended to index orientation, registration, attention and calculation, recall and language. The maximum possible score is 30 points, with a score <24 considered as an indication for cognitive decline or dementia [10]. Oxidative stress was estimated through MDA levels and SOD levels, MDA levels were detected by the thiobarbituric acid method and SOD levels were detected by the xanthine oxidase method. Expression levels of IL-1β, IL-17, amyloid beta proteins S100β and Aβ were compared between two groups before anesthesia, 1h after anesthesia and 1 day after operation. The inflammatory factors of IL-1β, IL-17, S100β and Aβ protein were objectively measured by ELISA method.

Statistical methods

SPSS19.0 statistical software was used for analysis in which the measurement data were expressed as "(x ± s)" and assessed by t test and the count data were assessed by χ^2 test, P<0.05 suggested that there was difference of statistical significance.

Results

Comparison of MMSE scores between the two groups at different time points

The MMSE scores in the two groups were significantly lower 1 h after anesthesia than those before anesthesia (P<0.05) in which cognitive function scores of the observation group were significantly higher than those of the control group (P<0.05) as shown in Table 1.

Comparison of SOD and MDA levels between the two groups at different time points

There was no statistically significant difference in superoxide dismutase (SOD) activity and malondialdehyde (MDA) score before anesthesia between the two groups (P>0.05). However, MDA levels were increased and SOD activity was decreased 1h after anesthesia and 1 day after operation, and the range of change was relatively small in observation group (P<0.05), as shown in Table 2.

Table 2. *Comparison of SOD and MDA levels between the two groups at different time points (mmol/ml).*

Group	MDA levels			SOD activity		
	Before anesthesia	1 h after anesthesia	1 d after operation	Before anesthesia	1 h after anesthesia	1 d after operation
Observation group	3.30 ± 1.20	4.92 ± 2.30	4.18 ± 2.01	46.92 ± 6.84	37.28 ± 4.11	40.02 ± 5.11
Control group	3.34 ± 1.19	7.00 ± 3.92	6.01 ± 3.09	47.21 ± 6.92	32.48 ± 4.80	33.40 ± 5.51
t	0.582	4.866	3.002	1.023	8.023	7.111
P	>0.05	<0.05	<0.05	>0.05	<0.05	<0.05

Table 3. *Comparison of IL-1β and IL-17 levels between the two groups at different time points.*

Group	IL-1β			IL-17		
	Before anesthesia	1 h after anesthesia	1 d after operation	Before anesthesia	1 h after anesthesia	1 d after operation
observation group	1.02 ± 0.42	1.30 ± 0.33	1.03 ± 0.53	1.23 ± 0.38	1.88 ± 0.83	1.53 ± 0.512.89 ± 1.022.828
control group	0.98 ± 0.40	1.99 ± 0.71	1.99 ± 0.42	1.27 ± 0.41	2.36 ± 1.00	<0.05
t	0.292	1.772	1.233	0.331	2.003	
P	>0.05	<0.05	<0.05	>0.05	<0.05	

Comparison of IL-1β and IL-17 levels between the two groups at different time points

In the observation group, the level of IL-1βand IL-17 1h after anesthesia and 1 day after operation was significantly lower than that in the control group (P<0.05), but with no significant difference of statistical value from that before anesthesia (P>0.05), while in the control group there was significant difference of statistical value in the level of IL-1βand IL-17 between 1h after anesthesia as well as 1 day after operation and that before anesthesia (P<0.05) (Table 3).

Comparison of level of amyloid beta proteins S100β and Aβ between the two groups at different time points

Compared with before anesthesia,the level of amyloid beta proteins S100β and Aβ increased significantly 1h after

anesthesia and 1 day after operation in the two groups with the increasing degree of the observation group significantly lower than that of the control group (P<0.05) (Table 4).

Table 4. Comparison of level of amyloid beta proteins S100β and Aβ between the two groups at different time points.

Group	S100β (μg/L)			Aβ (μg/mL)		
	Before anesthesia	1 h after anesthesia	1 d after operation	Before anesthesia	1 h after anesthesia	1 h after operation
Observation group	0.06 ± 0.02	0.07 ± 0.03	0.08 ± 0.04	5.11 ± 0.66	5.57 ± 1.04	5.59 ± 0.79
control group	0.05 ± 0.03	0.10 ± 0.03	0.17 ± 0.02	5.21 ± 0.67	6.61 ± 1.23	6.73 ± 1.21
t	0.223	1.072	1.233	0.331	4.582	3.028
P	>0.05	<0.05	<0.05	>0.05	<0.05	<0.05

Discussion

At present, the pathogenesis of liver cancer is not yet clear, but is generally believed to be associated with cirrhosis, viral hepatitis and aflatoxin, making certain impacts on patients, families as well as society [11,12]. Early detection and timely treatment is an important concept for liver cancer and it has played an important role in early diagnosis and treatment in the patients with in depth development of radical resection. The study has showed that in patients with early liver cancer treat by surgical resection, 1 year survival rate is about 80~90%, 3 year survival rate is about 60%~80%and 5 year survival rate is about 40%~60% [13,14], that is to say, the patients can generally live for more than 5 years after surgery. However, the operation itself causes great trauma with elevation of diaphragm and constrained respiratory movement in patients, which often affects the patients' respiratory and circulatory function, prognosis as well as quality of life. During operation the patients often undergo general anesthesia, which, as well as the trauma caused by surgery, will give rise to strong stress responses in patients. It, by acting on renin-angiotensin-aldosterone system as well as sympathetic-adrenal and the pituitary-adrenal system, gives rise to significantly elevated epinephrine level in patients, which enables to secrete large amounts of medulla hormone as well as cortical hormone and affects hemodynamic stability. Once the patient's stress reaction is excessive, it will cause complications like irregular heartbeats and heart failure in patients during perioperative period. Therefore, it is very important to choose appropriate narcotic drugs to solve the problem.

Sufentanil is a potent opioid analgesic and has advantages of low toxicity, wide dose range, strong analgesic effect, long duration and little influence on hemodynamics, thus being widely applied in thoracic operations. Propofol is a new fast short-acting intravenous anesthetic and can effectively relieve the stress during anesthesia [15,16]. But it has a certain inhibitory effect on the patient's breathing and is likely to cause lowering of blood pressure and even temporary respiratory arrest in severe cases. Intravenous injection of propofol can play the effect of fast onset, short duration as well as rapid recovery, and on this basis make lesser impacts in patient's breathing and circulatory function [17]. In this study, sufentanil intravenous constant injection and sufentanil intravenous constant injection with propofol target controlled infusion are applied in radical resection for liver cancer and the results showed that both two anesthesia methods have good analepsia quality. Besides In the clinic, Malondialdehyde (MDA) levels and superoxide dismutase (SOD) levels have often been treated as matching indicators, of which the SOD level was associated with free radical scavenging ability, whereas MDA reflected the degree of damage caused by free radicals to the cells [4]. The results showed that there was no statistically significant difference in superoxide dismutase (SOD) activity and malondialdehyde (MDA) score before anesthesia between the two groups (P>0.05). However, MDA levels were increased and SOD activity was decreased 1h after anesthesia and 1 day after operation, and the range of change was relatively small in observation group (P<0.05), suggesting that sufentanil combined can avoid excessive activation of oxidation and stress reaction, remove oxygen free radicel and keep from excessive consumption of antioxidant compounds.

Postoperative cognitive dysfunction refers to the disorder of consciousness, cognition and memory before and after the operation and is frequently tested by MMSE in clinical practices [17]. The results of this study also showed that the MMSE scale scores decreased 1h after the anesthesia in both two groups, which indicates that intraoperative anesthesia can lead to cognitive impairment in patients but appropriate method can significantly reduce its extent. The changes of S100β level can reflect the severity as well as prognosis of brain injury and play a certain role in learning and memory process. Typically, when there is cell trauma in central nervous system or permeability of blood brain barrier is increased, S100β would seep from the cytosol into the cerebrospinal fluid and enter bloodstream through the damaged blood-brain barrier [18]. It can be seen in this study that the S100β level at 1h after anesthesia and 1d after operation is higher than that before anesthesia with the level at 1h after anesthesia as the peak, which suggests the elderly patients with liver cancer would suffer from different degrees of brain damages after going through radical resection. Aβ is a protein of senile dementia characteristics and is associated with cognitive impairment. In this study diseases like diabetes and central nervous system diseases which will affect the metabolism of Aβ protein were

excluded and it turned out that the level of Aβ protein at 1h after anesthesia and 1 day after operation was higher than that before anesthesia with the level at 1h after anesthesia as the peak. In the two groups, the increased level of the observation group was lower. In addition, compared with the control group, the IL-1β and IL-17 level of the observation group at 1h after anesthesia and 1d after operation was closer to that before anesthesia, indicating that sufentanil combined with propofol has certain effects of immune inhibition, highly selective activation of receptors and inhibiting sympathoblast impulse as well as inflammatory reaction.

To sum up, during radical resection for liver cancer, both two methods of anesthesia will affect patient's postoperative cognitive function to a certain extent, but sufentanil combined with propofol target controlled infusion has relatively smaller effect and better inhibits stress response in patients after anesthesia, thus serving as an ideal method of anesthesia and analgesia. There were certain limitations in the research. First, the number of samples was small and brought selection bias. Second, we did not investigate anesthetic effect with different concentrations. In the future studies, large samples and multi aspects will be conducted to explore the effectiveness of sufentanil combined with propofol.

References

1. Bastani R, Glenn BA, Taylor VM. Integrating theory into community interventions to reduce liver cancer disparities: The Health Behavior Framework. Prev Med 2016; 50: 63-67.
2. Wáng YXJ, Baere TD, Idée JM. Transcatheter embolization therapy in liver cancer: an update of clinical evidences. Chinese J Cancer Res (English Edition) 2015; 27: 96.
3. Bajwa SJ, Anand S, Kaur G. Anesthesia and cancer recurrences: The current knowledge and evidence. J Cancer Res Ther 2015; 11: 528-534.
4. Li XD, Sun GF, Zhu WB, Wang YH. Effects of high intensity exhaustive exercise on SOD, MDA, and NO levels in rats with knee osteoarthritis: Genet Mol Res 2015; 14: 12367-12376.
5. Falksom G, Moertel CG, Lavin P. Chemotherapy studies in primary liver cancer: A prospective randomized clinical trial. Cancer 2015; 42: 2149-2156.
6. Planinsic RM, Hilmi IA, Sakai T. Liver transplantation anaesthesia. Clin Transplant 2014; 28: 540-545.
7. Zhou JN, Zeng Q, Wang HY. MiR-125b attenuates epithelial-mesenchymal transitions and targets stem-like liver cancer cells through SMAD2 and SMAD4. Hepatology 2015.
8. Oliver N, Bohorquez H, Anders S. Post-liver transplant delirium increases mortality and length of stay. Ochsner J 2017; 17: 25.
9. Fei W, Zou ZR, Dong Y. Correlation between serum S100β protein levels and cognitive dysfunction in patients with cerebral small vessel disease: a case-control study. Biosci Rep 2017; 37: BSR20160446.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state"- A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975; 12: 189-198.
11. Ryerson AB, Eheman CR, Altekruse SF. Annual report to the nation on the status of cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016; 122: 1312-1337.
12. Zhou J, Zeng Q, Wang H. MicroRNA-125b attenuates epithelial-mesenchymal transitions and targets stem-like liver cancer cells through small mothers against decapentaplegic 2 and 4. Hepatology 2015; 62: 801.
13. Buggy DJ, Hemmings HC. Special issue on anaesthesia and cancer. Bja Br J Anaesth 2014; 113: i1-i3.
14. Hedenqvist P, Jensen-Waern M, Fahlman A. Intravenous sufentanil-midazolam versus sevoflurane anaesthesia in medetomidine pre-medicated Himalayan rabbits undergoing ovariohysterectomy. Vet Anaesth Analgesia 2015; 42: 377-385.
15. Reupke V, Walliser K, Perl T. Total intravenous anaesthesia using propofol and sufentanil allows controlled long-term ventilation in rabbits without neuromuscular blocking agents. Laboratory Animals 2016.
16. Modak SD, Kane DG. Conscious sedation for balloon mitral valvotomy: A comparison of fentanyl versus sufentanil. Annal Cardiac Anaesth 2017; 20: 163.
17. Alexander R, Booth J, Olufolabi AJ. Comparison of remifentanil with alfentanil or suxamethonium following propofol anaesthesia for tracheal intubation. Anaesthesia 2015; 54: 1032-1036.
18. Bourassa J, Hutchinson K, Dilks L. A validity study: A comparison of the folstein mini mental state examination (MMSE) to the montreal cognitive assessment (MoCA). J Head Trauma Rehab 2013; 28: E56-E57.

***Correspondence to**

Jing Li

Honghui Hospital

Xi'an Jiaotong University

PR China