

Original Article

Effects of Sevoflurane or Propofol on Immune Function in Patients Undergoing Hepatectomy

Hao Gao¹, Jin-Chao Song^{1*}, Jin-Min Zhang¹, Ying-Fu Jiao¹, Zhi-Jie Lu¹, Tian-Zhu Tao², and Wei-Feng Yu¹

ABSTRACT

Background: In this study, the effects of sevoflurane or propofol on immune function in patients undergoing partial hepatectomy were investigated during general anesthesia and after surgery.

Methods: Seventy-two patients undergoing hepatectomy were randomized into sevoflurane group or propofol group. Sevoflurane or target-controlled infusion (TCI) of propofol was separately used to anesthesia induction and maintenance of two groups. Venous blood samples were taken before induction, 2 hours after anesthesia and 2 hours after surgery for measurement of the percentages of T lymphocyte (CD3⁺, CD4⁺, CD8⁺) and NK cells.

Results: Compared with that before anesthesia induction, percentage change in CD3⁺ and CD4⁺ T cells to baseline was -0.7% and 3.8% in sevoflurane group, 10.2% and 20.2% in propofol group 2 hours after anesthesia (P=0.002 for CD3⁺ T cells and P=0.029 for CD4⁺ T cells). Percentage change in NK cells was 17.6% in sevoflurane and -12.2% in propofol group 2 hours after anesthesia respectively (P=0.03). There was no significant difference in percentage change 2 hours after surgery of T cells and NK cells to baseline between two groups.

Conclusions: Our study indicates that use of propofol during general anesthesia tend to increase the percentages of peripheral CD3⁺ and CD4⁺ cells, while sevoflurane increase the peripheral NK cells.

From ¹Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; ²Department of Anesthesiology, Air Force General Hospital of the Chinese PLA, Beijing, China.

*Contributed equally to this work.

Correspondence to Dr. Wei-Feng Yu at ywf808@yeah.net.

Citation: Hao Gao, Jin-Chao Song, Jin-Min Zhang, Ying-Fu Jiao, Zhi-Jie Lu, Tian-Zhu Tao, et al. Effects of sevoflurane or propofol on immune function in patients undergoing hepatectomy. *J Anesth Perioper Med* 2017; 1: 1-6.

The effects of anesthetics on immune function have been a major concern for anesthesiologists in the last decade. The published studies indicate that the anesthetics could directly inhibit immune function of patients, which is closely related with tumor recurrence (1). Aside from the inhibition of anesthetics on lymphocytes, some reports also suggested that anesthetics had a capability to inhibit growth of tumor cells (2-4).

In the anti-tumor process, the cell immunity induced by T-lymphocytes plays a very important role. The cytotoxic T

cells (CTL), is identified as the major effect or cell in the immune response against liver cancer. And CD4⁺ Th cells enhance anti-tumor CTL responses by enhancing clonal expansion at the tumor site, preventing activation-induced cell death and functioning as antigen-presenting cells for CTL. NK cells have the ability to kill circulating tumor cells of almost any origin, and the presence of NK cells in tumor environment is associated with patients' outcome. Since increasing number of studies has been conducted to determine the role of anesthetics in the regulation of circulating

lymphocytes, evidence is rather limited with respect to the difference between intravenous anesthetics and volatile anesthetics. It was noteworthy that the inhibition of inhalation anesthetics on immune function seemed to be greater than that of intravenous anesthetics (5), as evidenced by decreased numbers of peripheral T cells in patients receiving inhalation anesthesia compared to those patients exposed to intravenous anesthesia.

The previously published studies focused mainly on the impacts of anesthesia on patients undergoing the excision of breast cancer or prostate cancer (1, 6, 7), a cohort had a relatively high 5-year survival rate. To date, it remains unknown whether inhalation anesthetics or intravenous anesthetics have the similar effects on the immune function in liver cancer patients undergoing hepatectomy. In the present study, the effects of propofol or sevoflurane on percentage change of peripheral immune cells in patients undergoing liver resection were investigated during anesthesia and after surgery. We hypothesize propofol may have more favorable effects on the immune function than sevoflurane.

METHODS

The study was approved by the institutional research ethics committee of Eastern Hepatobiliary Surgery Hospital in Shanghai, China (EHBH-KY-2015-01-009). The registration number of

randomized clinical trials is ChiCTR-IPR-15006841. After obtaining written, informed consent, Seventy-two patients undergoing hepatectomy for liver cancer were randomized into sevoflurane group or propofol group. All patients were ASA physical status I to III. Exclusion criteria included known or suspected cardiac, pulmonary disease, weight beyond 20% of ideal, age older than 70 years or younger than 18 years, a recent history (<2 weeks) of blood transfusion, immunosuppressive drug therapy, ascites, renal insufficiency (creatinine concentration >1.5 mg/dl) and a recent history (<1 month) of infection and fever.

All patients received intramuscular injection of atropine (0.5 mg) and oral midazolam (5.0 mg) before surgery. An arterial catheter was placed for measurement of arterial blood pressure. A central venous catheter was inserted into an internal jugular vein for infusion of drug or fluids and CVP monitoring. BIS (BIS™ XP sensor), heart rate (HR), invasive arterial blood pressure, electrocardiogram, end-tidal carbon dioxide, and oxyhemoglobin saturation were monitored continuously throughout the study (Philips HP Viridia 24/26M1205A). The room temperature was controlled at 23°C, and a heating blanket was maintained at 37.8°C during the procedure.

The patients was induced with by sufentanil (0.4 µg/kg), and target-controlled infusion of propofol (4.0 µg/ml) in the propofol group, or sevoflurane (8%) in the sevoflurane group. The patients received 0.2 mg/kg cisatracurium after BIS value reach 60, and 3 minutes later tracheal intubation was performed. After intubation, anesthesia was maintained with propofol (TCI, 2-4 µg/ml) or sevoflurane (1.5-2.5%) respectively. Sufentanil (0.2-0.4 µg/kg) and cisatracurium (5-10 mg) were administered intermittently depending on surgery demands. BIS value was adjusted to about 40.

Ringers lactate solution and hydroxyethyl starch 6% (130/0.4) were used to maintain CVP between 5 to 12 cm H₂O. Blood products (fresh frozen plasma and packed red blood cells) were transfused when necessary to maintain a haemoglobin value >7.0 mg/dl. An appropriate dose of metaraminol was given once the mean arterial pressure (MAP) was below 60 mm Hg.

Blood samples were taken at the designated time points: T₀=baseline values, before induction of anesthesia; T₁=2 hours after anesthesia, or at the time

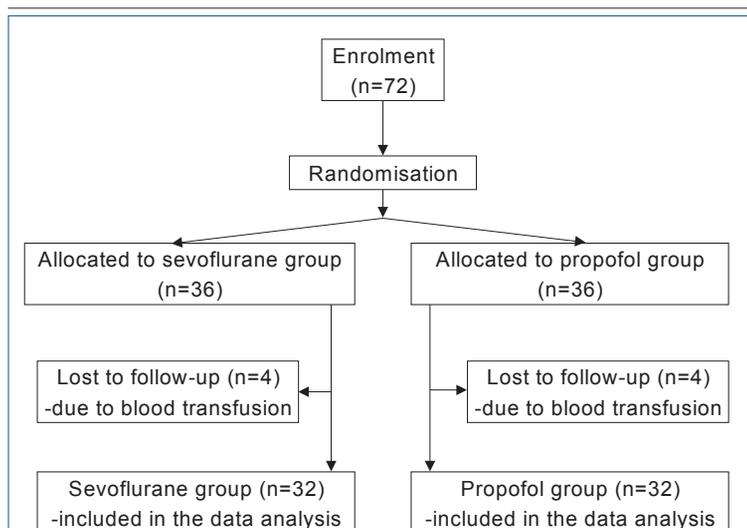


Figure 1. Flow Diagram.

when anesthesia was stopped if the operation time was less than 2 hours; $T_2=2$ hours after surgery. The level of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells and NK cells were determined by flow cytometry. Fluorescently-labeled antibodies were all purchased from BD Multitest™ IMK. Percentage change 2 hours after anesthesia = (level of immune cells at T_1 -level of immune cells at T_0)/level of immune cells at T_0 *100%. Percentage change 2 hours after surgery = (level number of immune cells at T_2 - level of immune cells at T_0)/level of immune cells at T_0 *100%. The effects of propofol or sevoflurane on liver and kidney function defined by peak alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr) and blood urea nitrogen (BUN) over 6 days post-operation. All outcome variables of liver and kidney function were measured before and 1, 3, and 6 days after surgery. Additional indexes were peak values of white blood cells (WBC), bilirubin, length of hospital stay and perioperative complications.

The estimation of sample size is based on our pre-test. The average percentage change of the number of $CD3^+$ cells at 2 hours after anesthesia to baseline were presented as 9.3% (15.1%) ($n = 11$) and -1.7% (15.1%) ($n=11$) in the propofol group and the sevoflurane group, respectively. According to the formula ($n=15.7/ES^2 + 1$), sample size was calculated (8). The minimum of 31 of patients in each group is sufficient for testing ($\alpha=0.05$, and power=0.8).

All data in the text and tables are expressed as mean \pm SD, number (n) or percentage. Continuous outcomes with normal distribution were analyzed with independent 2-sample t-test. The frequency data were compared using the χ^2 test or Fisher's exact test or Continuity correction as appropriate. Reported P value was 2-sided, with $P<0.05$ considered statistically significant. All analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL).

RESULTS

The study was completed without any significant clinical complication. A total of 8 patients were excluded from study due to blood transfusion. The remaining 64 patients were included in final data analysis, including 32 patients in sevoflurane group, and 32 patients in propofol group

Table 1. Patient Characteristics and Preoperative Laboratory Values

	Sevoflurane group (n=32)	Propofol group (n=32)
Age (yrs)	52.5 (10.6)	56.3 (11.9)
Body height (cm)	167.3 (6.7)	167.6 (6.5)
Weight (kg)	64.1 (8.2)	66.2 (9.2)
Gender (male/female)	24/6	24/6
Baseline Cr ($\mu\text{mol/l}$)	64.0 (15.1)	70.3 (9.8)
Baseline BUN (mmol/l)	4.9 (1.3)	5.4 (1.1)
Baseline bilirubin ($\mu\text{mol/l}$)	16.2 (7.2)	14.6 (6.2)
Baseline ALT (U/l)	41.2 (33.7)	33.3 (24.6)
Baseline AST (U/l)	38.9 (23.4)	34.6 (19.7)
Baseline Albumin (g/L)	42.1 (4.2)	43.2 (4.5)
Baseline WBC count ($\times 10^3/\text{mL}$)	5.0 (1.6)	5.5 (2.0)

Data are expressed as mean (standard deviation). ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Cr=creatinine.

Table 2. Intraoperative Data and Length of Hospital Stay.

	Sevoflurane group (n=32)	Propofol group (n=32)	P
Operation time (min)	151.0 (55.1)	146.9 (40.8)	0.749
Pringle time (min)	9.1 (9.3)	11.4 (8.7)	0.368
Blood loss (ml)	258.7 (232.8)	201.4 (147.8)	0.291
Hospital stay (days)	16.1 (8.6)	14.9 (8.5)	0.578

Data are expressed as mean (standard deviation).

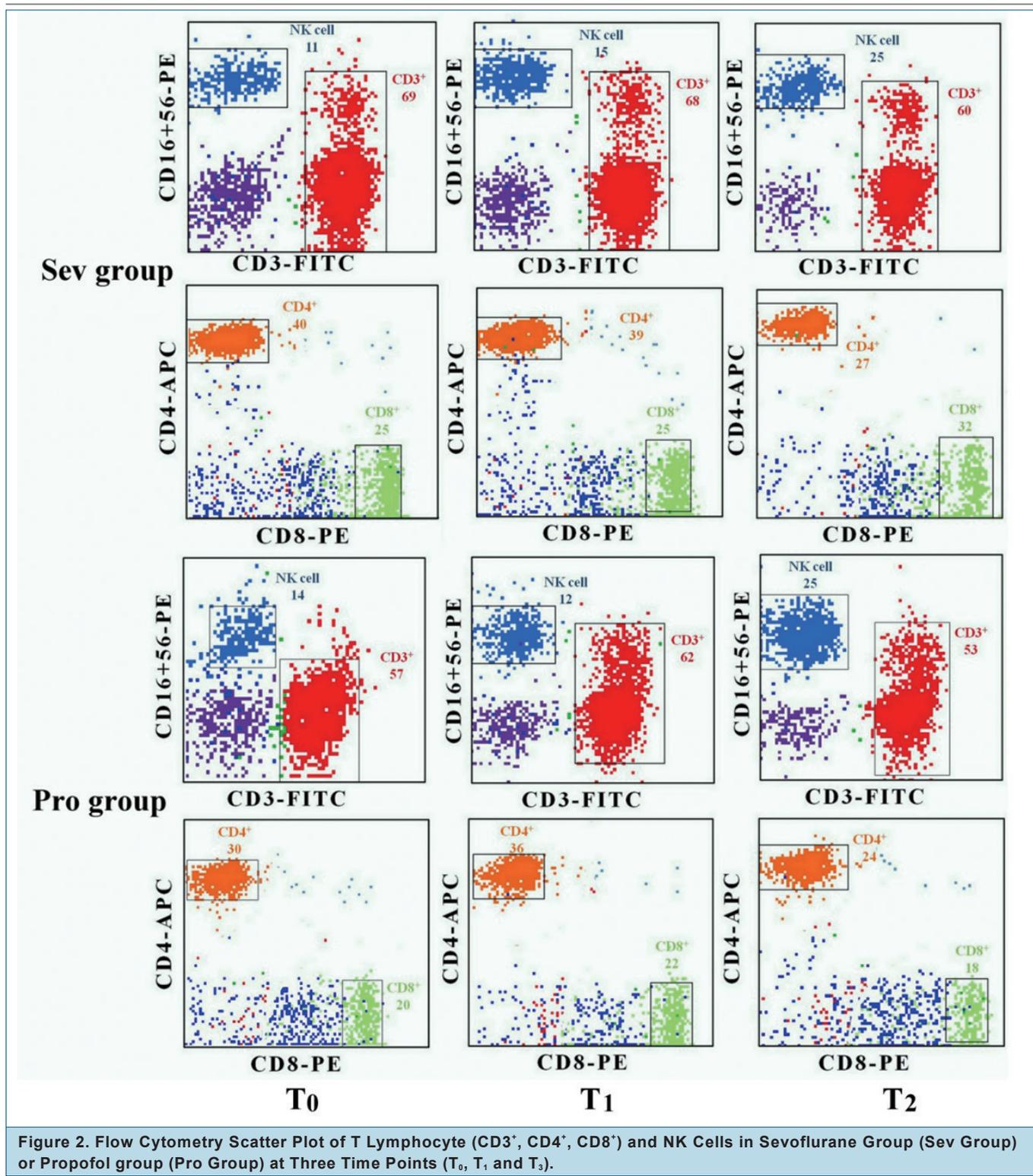
Table 3. The Average Percent Change of the Number of Immune Cells to Baseline.

	Sevoflurane group (n=32)	Propofol group (n=32)	P
Percentage change 2 hours after anesthesia (%)			
$CD3^+$	-0.7 (11.9)	10.2 (14.6)	0.002
$CD4^+$	3.8 (21.5)	20.2 (35.3)	0.029
$CD8^+$	-1.2 (12.0)	1.5 (13.0)	0.399
NK $^+$	17.6 (67.4)	-12.2 (42.2)	0.030
Percentage change 2 hours after surgery (%)			
$CD3^+$	-8.7 (10.2)	-4.7 (12.7)	0.166
$CD4^+$	-8.1 (38.4)	-11.5 (20.1)	0.638
$CD8^+$	-1.0 (24.7)	-1.9 (16.7)	0.862
NK $^+$	51.3 (44.0)	39.5 (42.8)	0.270

Data are expressed as mean (standard deviation). $P<0.05$ indicates statistically significant difference between two groups.

(Figure 1). There was no significant difference in patients' characteristics, preoperative laboratory values, intraoperative data and length of hospital stay between two groups (Table 1 and 2).

As shown in table 3, percentage change 2 hours after anesthesia in $CD3^+$, $CD4^+$ T and $CD8^+$ T cells to baseline was 10.2%, 20.2% and 1.5% in propofol group, -0.7%, 3.8% and -



1.2% in sevoflurane group, respectively (P=0.002 for CD3⁺ T cells; P=0.029 for CD4⁺ T cells ; P=0.399 for CD8⁺ T cells). Percentage change 2 hours after anesthesia in NK cells was

17.6% in sevoflurane compared to - 12.2% in propofol group (P=0.03), suggesting that the number of circulating NK cells tended to be decreased in propofol anesthesia, while it was in-

creased in sevoflurane anesthesia.

There was no significant difference in percentage change 2 hours after surgery of T cells and NK cells to baseline between sevoflurane group and propofol group (Figure 2). Compared with -8.7%, -8.1%, -1.0% and 53.1% in sevoflurane group, percentage change 2 hours after surgery of CD3⁺, CD4⁺, CD8⁺ T cells and NK cells to baseline was -4.7%, -11.5%, -1.9% and 39.5% in propofol group.

The Cr, BUN, bilirubin, ALT, AST, WBC and nadir albumin over 6 postoperative days were showed in table 4. There was no significant difference between the two groups. There were no deaths and hepatic failure during our study.

DISCUSSION

In the present study, the effects of sevoflurane and propofol on immune function were investigated in patients undergoing liver resection during and after anesthesia. Our results showed that percentage change in CD3⁺ and CD4⁺ T cells 2 hour after anesthesia was significantly increased in propofol group compared with sevoflurane group, while the NK cells were significantly reduced. There was no significant difference in percentage change of immune cells 2 hour after surgery between the groups. These data implied that propofol significant increase peripheral blood CD3⁺ and CD4⁺ T cells and sevoflurane significant increase peripheral blood NK cells during anesthesia.

In this study, patients' characteristics, preoperative laboratory values, intraoperative data and length of hospital stay between two groups were comparable between the two groups. It is believed that opioids may change patients' immune function during the peri-operative period (9). In present study, the consumption of opioids in two groups were similar, therefore, the effect of opioids on immune function should be comparable. Considering that peri-operative blood transfusion could also change immune function in cancer patients to some extent (10, 11), we excluded the eight patients receiving perioperative blood transfusion in surgery.

The effects of propofol on immune function have been investigated in recent years. Mammoto et al. showed that clinically relevant concentrations of propofol (1-5 µg/ml) decreased the inva-

	Sevoflurane group (n=32)	Propofol group (n=32)	P
Peak Cr (µmol/l)	65.8 (12.9)	71.1 (10.4)	0.091
Peak BUN (mmol/l)	7.5 (1.5)	6.8 (1.5)	0.100
Peak bilirubin (µmol/l)	33.9 (18.5)	31.1 (16.3)	0.550
Peak ALT (U/l)	322.8 (303.2)	377.4 (330.7)	0.525
Peak AST (U/l)	346.2 (333.7)	480.7 (405.3)	0.185
Nadir albumin (g/l)	33.9 (3.2)	34.2 (3.1)	0.773
Peak WBC count (¹⁰ ³ /ml)	14.7 (4.7)	21.6 (27.8)	0.218

Data are expressed as mean (standard deviation). ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Cr=creatinine.

sion ability of human cancer cells (HeLa, HT1080, HOS and RPMI-7951) *in vitro*, and furthermore, propofol induced lung metastasis of tumor cells in a mouse model of osteosarcoma (12). Siddiqui RA et al. showed that the propofol-DHA or propofol-EPA conjugates significantly inhibit adhesion, migration and induced apoptosis of breast cancer cells, implying that these conjugates may be useful for the treatment of breast cancer (6). However, there are some different results, demonstrating that propofol could enhance the migration of human breast cancer cell lines (13).

Activation of a substantial number of T lymphocytes is an important step in anti-infective and anti-tumor perioperative immune response. In Schneemilch's study, CD3⁺ and CD4⁺ cells increased 2 hour after propofol anesthesia but decreased on the 3 day post-operation. However, the absolute number of T lymphocytes (CD3⁺, CD4⁺, CD8⁺) decreased 2 hours after sevoflurane anesthesia and until the third postoperative days (5). Besides these, the results from Ren et al. study showed that propofol promoted activation and differentiation of peripheral T-helper cells. The percentage of CD4(+)CD28(+) and the ratio of INF-γ:IL-4 increase with propofol but showed no change with isoflurane in patients undergoing pulmonary lobectomy for non-small-cell lung cancer (14). Inada et al. found in patients undergoing craniotomy that propofol may be better than isoflurane in attenuating the surgical stress-induced adverse immune response (15). In this study, we reported that propofol anesthesia but not sevoflurane anesthesia could increase peripheral CD3⁺ and CD4⁺ cells in patients undergoing liver resection. We suppose that the increased circulating T lymphocytes may be helpful

in inhibition of tumor spread. Our study was consistent with previous research, but further studies are needed to explain its mechanisms.

Volatile anesthetic was believed to have an adverse effect on human immune response in several studies. In Brand's study, there was a significant decrease of circulating NK cells during general anesthesia with isoflurane, thiopental and fentanyl (16). Moreover, inhaled anesthetics had a negative effect on cytotoxicity of natural killer cells and NK-like cells, indicated by altered cytokine release (17). Besides these, sevoflurane was shown to suppress anti-tumor immunity through inhibiting the release of cytokine such as IL-1B\TNF- α from NK cells in vitro (18, 19). On the contrary, the effects of propofol on NK cell immune function was different from volatile anesthetic. Serum from women undergoing breast cancer surgery with propofol-paravertebral block anesthetic led to greater human donor NK cells cytotoxicity in vitro compared with serum from women who received sevoflurane-opioid anesthetic (20). In Melamed's study, although propofol caused a significant decrease in the number of NK cells compared with the control group, propofol did not significantly suppressed NK activity (21). In our research, we also found that propofol could decrease peripheral NK cells 2 hour after anesthesia but increased on the 2 hour post-operation in patients undergoing liver resection. Peripheral NK cells continue to increase at least 2 hour post-operation with sevoflurane anesthe-

sia. This finding is inconsistent with a forementioned research, where in NK cells were decreased during volatile anesthesia. The differences in patients' clinicopathologic characteristics across studies may account for the observed variation.

This study has some limitations. First, this study only compared the effects of propofol and sevoflurane on T lymphocytes and NK cells in peripheral blood, their functional status of these target immune cell subsets was not investigated. Second, the CD4⁺ cell subtypes were not assessed in the present study. Third, The effect of propofol and sevoflurane on long-term outcome of patients undergoing liver resection needs to be further investigated in future study. Hence, further studies are still required to confirm whether different anesthetics will influence immune function of patients.

In conclusion, our study indicates that propofol anesthesia tend to increase the peripheral CD3⁺ and CD4⁺ cells, while sevoflurane has the ability to increase the peripheral NK cells. Since the effects of anesthetics on the long term outcomes are out of scope in this study, it remains unknown whether propofol or sevoflurane anesthesia is better in patients with liver cancer.

This study was supported by a grant from the National Natural Science Foundation of China: (NSFC, No.81371511 and No.31171013).

All authors have no other potential conflicts of interest for this study to declare.

References

- Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 2008;109:180-7.
- Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesth Analg* 2010;110:1630-5.
- Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, et al. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway in vitro. *Anesthesiology* 2013;119:593-605.
- Xie Z. Cancer prognosis: can anesthesia play a role? *Anesthesiology* 2013;119:501-3.
- Schneemilch CE, Ittenson A, Ansoorge S, Hachenberg T, Bank U. Effect of 2 anesthetic techniques on the postoperative proinflammatory and anti-inflammatory cytokine response and cellular immune function to minor surgery. *J ClinAnesth* 2005;17:517-27.
- Siddiqui RA, Zerouga M, Wu M, Castillo A, Harvey K, Zaloga GP, et al. Anticancer properties of propofol-docosahexaenoate and propofol-eicosapentaenoate on breast cancer cells. *Breast Cancer Res* 2005;7:R645-54.
- Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006;105:660-4.
- Lerman J. Study design in clinical research: sample size estimation and power analysis. *Can J Anaesth* 1996;43:184-191.
- Roy S, Wang J, Kelschenbach J, Koodie L, Martin J. Modulation of immune function by morphine: implications for susceptibility to infection. *J Neuroimmune Pharmacol* 2006;1:77-89.
- Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006; 1: CD005033.
- Atzil S, Arad M, Glasner A, Abiri N, Avraham R, Greenfeld K, et al. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. *Anesthesiology* 2008;109: 989-97.
- Mammoto T, Mukai M, Mammoto A, Yamanaka Y, Hayashi Y, Mashimo T, et al. Intravenous anesthetic, propofol inhibits invasion of cancer cells. *Cancer Lett* 2002;184:165-70.
- Garib V, Lang K, Niggemann B, Zänker KS, Brandt L, Dittmar T. Propofol-induced calcium signalling and actin reorganization within breast carcinoma cells. *Eur J Anaesthesiol* 2005;22: 609-15.
- Ren XF, Li WZ, Meng FY, Lin CF. Differential effects of propofol and isoflurane on the activation of T-helper cells in lung cancer patients. *Anaesthesia* 2010;65:478-82.
- Inada T, Yamanouchi Y, Jomura S, Sakamoto S, Takahashi M, Kambara T, et al. Effect of propofol and isoflurane anaesthesia on the immune response to surgery. *Anaesthesia* 2004;59:954-9.
- Brand JM, Kirchner H, Poppe C, Schmucker P. The effects of general anesthesia on human peripheral immune cell distribution and cytokine production. *Clin Immunol Immunopathol* 1997;83:190-4.
- Santamaria LB, Schifilliti D, La Torre D, Fodale V. Drugs of anaesthesia and cancer. *Surg Oncol* 2010;19:63-81.
- Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth* 2010;105:106-15.
- Mitsuhata H, Shimizu R, Yokoyama MM. Suppressive effects of volatile anesthetics on cytokine release in human peripheral blood mononuclear cells. *Int J Immunopharmacol* 1995;17:529-34.
- Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. *Br J Anaesth* 2014;113 Suppl 1:i56-62.
- Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg* 2003;97:1331-9.