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Effects of propofol and sevoflurane on perioperative immune response in patients undergoing laparoscopic radical hysterectomy for cervical cancer

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Abstract

The aim of this study is to compare the effects of propofol and sevoflurane anesthesia on perioperative immune response in patients undergoing laparoscopic radical hysterectomy for cervical cancer.

Sixty patients with cervical cancer scheduled for elective laparoscopic radical hysterectomy under general anesthesia were randomized into 2 groups. TIVA group received propofol induction and maintenance and SEVO group received sevoflurane induction and maintenance. Blood samples were collected at 30 min before induction (T_0); the end of the operation (T_1); and 24 h (T_2), 48 h (T_3), and 72 h (T_4) after operation. The T lymphocyte subsets (including CD3+ cells, CD4+ cells, and CD8+ cells) and CD4+/CD8+ ratio, natural killer (NK) cells, and B lymphocytes were analyzed by flow cytometry.

After surgery, all immunological indicators except CD8+ cells were significantly decreased in both groups compared to basal levels in T_0, and the counts of CD3+ cells, CD4+ cells, NK cells, and the CD4+/CD8+ ratios were significantly lower in the SEVO groups than that in the TIVA group. However, the numbers of B cells were comparable at all the time points between 2 groups.

Laparoscopic radical hysterectomy for cervical cancer is associated with postoperative lymphopenia. In terms of protecting circulating lymphocytes, propofol is superior to sevoflurane.

Abbreviations: ANOVA = analysis of variance, ASA = American Society of Anesthesiologists, BIS = bispectral index, CMI = cell-mediated immunity, ECG = electrocardiography, HPA = hypothalamic–pituitary–adrenal, NK = natural killer, $P_{ET}CO_2$ = end-tidal carbon dioxide.

Keywords: cervical cancer, immunity, laparoscopic radical hysterectomy, lymphocyte, propofol, sevoflurane

1. Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide. In contrast to the decreasing incidence trends in developed countries, a substantial increase in cervical cancer incidence was seen in China.[1,2]

For cervical cancer, radical surgery is one of the mainstays of treatment. However, surgery and anesthesia induced perioperative immunosuppression has been implicated in the development of postoperative complications, such as delayed wound healing, systemic inflammatory response and other septic events. Furthermore, impaired immune system may allow malignant cell to overcome host immunosurveillance so that a window is created for cancer metastasis and recurrence during perioperative period.[3–5]

Laparoscopic surgery is associated with lower surgical morbidity in terms of less intraoperative blood loss, shorter hospital stay, earlier resumption of daily activities, and increased quality of life.[6,7] And after a long-term disputes and practice, laparoscopic radical hysterectomy for cervical cancer has been accepted by most researchers.[8] Reports have suggested that laparoscopic surgery has greater ability for preservation of lymphocytes number and function than conventional open surgery.[9,10] Against this background, the effects of different anesthesia techniques and anesthetics on perioperative immune response become more prominent.

Propofol and sevoflurane are most widely used anesthetics for general anesthesia. It has been reported that compared with sevoflurane, propofol could better attenuate the surgical stress-induced adverse immune response, have more protective effects for circulating lymphocytes and provide better short-term consequence in patients receiving cancer or cardiac surgery.[11–13] Besides, Enlund et al[14] showed a higher overall 1-year survival rate in patients after radical colon and breast cancer surgery

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under general anesthesia with propofol than patients given sevoflurane. Nevertheless, there is no study has evaluated the effects of propofol and sevoflurane on perioperative immune response in patients undergoing laparoscopic radical hysterectomy for cervical cancer.

In this study, we compared the effects of propofol and sevoflurane anesthesia on peripheral lymphocyte counts, including CD3+, CD4+, CD8+, B, natural killer (NK) cells, and CD4+/CD8+ ratio in patients with cervical cancer who were scheduled for elective laparoscopic radical hysterectomy. We hypothesized that propofol would provide more protection for the circulating lymphocytes than sevoflurane during perioperative period.

2. Methods

The study was approved by the Ethics Committee of the Xuzhou Central Hospital. Written informed consent was obtained from all participants before the trial. Female patients classified as American Society of Anesthesiologists (ASA) physical status I to II and ages 30 to 65 years who had cervical cancer requiring radical surgery were recruited. All the patients were scheduled for elective laparoscopic radical hysterectomy under general anesthesia. None had a history of endocrine, immune, or circulatory system diseases. Other exclusion criteria included recent or concurrent chemotherapy, a requirement for perioperative blood transfusion, perioperative treatment with immunomodulatory agents and any contraindication to drugs used in this study. Patients who developed major surgical complications were also excluded from our study.

Sixty patients were enrolled and were randomly allocated to 2 groups using a computer-generated randomization list. None of the patients received any premedication. After the patients arrived in operating room, the radial artery was cannulated for invasive blood pressure monitoring. The electrocardiography (ECG), peripheral capillary oxygen saturation, end-tidal carbon dioxide ($P_{ET}CO_2$), and bispectral index (BIS) were also continuously monitored during the operation. In the propofol induction and maintenance (TIVA) group, anesthesia was induced with midazolam 2 mg, propofol 2.0 to 2.5 mg/kg (Diprivan, AstraZeneca, Zug, Switzerland), fentanyl 2 to 3 μg/kg, and maintained with propofol 4 to 8 mg/kg per h. The sevoflurane induction and maintenance (SEVO) group was induced with midazolam 2 mg, inhalation of 8% sevoflurane (Sevofrane, Maruishi, Osaka, Japan) with fresh gas flow 5 L/min, fentanyl 2 to 3 μg/kg, and maintained with inhalation of 2% to 3% sevoflurane. Rocuronium 0.6 mg/kg was given to all patients to facilitate tracheal intubation. The lungs were ventilated with oxygen in air (50–60%). Mechanical ventilation was administered to maintain a $P_{ET}CO_2$ concentration of 35 to 40 mm Hg. After induction, continuous infusion of remifentanil 0.1 to 0.2 μg/kg/min and cisatracurium 0.2 μg/kg/min were administered in all patients. The depth of anesthesia was monitored by BIS monitor and the concentration of sevoflurane or infusion rate of propofol was adjusted to keep the BIS between 40 and 60. Thirty minutes before the end of surgery, fentanyl 1 to 2 μg/kg was administered as an intravenous bolus in every patient. All patients received patient-controlled intravenous analgesia for postoperative pain therapy.

Two milliliters of peripheral venous blood was collected into anticoagulant test tubes (ethylenediaminetetraacetic acid tube) at 5 time points: 30 min before induction of anesthesia (T_0); the end of the operation (T_1); and 24 h (T_2), 48 h (T_3), and 72 h (T_4) after operation. Vacutainer tubes were transported to the hematology laboratory immediately.

Lymphocyte subsets were analyzed on a FACScalibur Flow Cytometer (Becton, Dickinson and Company, Franklin Lakes, NJ). A single-platform, lyse-no-wash procedure was performed with Trucount tubes (BD, Franklin, NJ) with the following 2- or 4-color monoclonal antibody combinations supplied in the MultiTEST IMK kit (BD): CD3FITC/CD8PE/CD45PerCP/CD4APC or CD3FITC/CD16 + 56PE/CD45PerCP/CD19APC. The stained blood sample was lysed with a diluted lysing solution, and special care was taken not to expose the stained sample to light. CD3+ T cells, CD4+ T helper cells, and CD8+ T cytotoxic cells were identified according to published protocols.[15] B cells were identified by CD19 expression, and NK cells were identified by the CD3− CD16+ and/or CD56+ phenotype.

During the perioperative period, the surgical details of every patient (i.e., operation time, blood loss, the volume of crystalloid or colloid received, urine volume, and intraoperative complications) and the postoperative characteristics (i.e., duration of catheterization, hospital stay period, and postoperative complications) were recorded.

We believe that the CD4+/CD8+ ratio 24 h after surgery is a more useful indicator for assessing immune system function. From published study,[15] the mean CD4+/CD8+ ratio before induction of anesthesia was estimated at about 1.5 (with standard deviation [SD] approximately 0.56). We considered that a difference of 0.5 would be clinically important. We judged that 27 patients in each group would be required to detect this difference with a power of 0.90 at a significance level of 0.05 (2-sided). To allow for 10% loss during the study period, recruitment of a total of 60 patients was intended. The results of this study were evaluated using the GraphPad Prism 5.0 (GraphPad Software Inc, San Diego, CA). Continuous variables were described as mean ± SD and differences between groups were analyzed by using unpaired *t* test for normally distributed data. Categorical variables were described as number (%) and analyzed by Fisher exact test. The differences of lymphocyte subsets counts across different time point in the same group were analyzed by 1-way analysis of variance (ANOVA) followed by post hoc Tukey HSD test. The differences of lymphocyte subset counts between groups according to the time points were analyzed by 2-way ANOVA followed by Bonferroni correction. P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Patient recruitment

Patient recruitment took place from March 1, 2014 to August 1, 2014. A total of 70 patients with cervical cancer scheduled to undergo laparoscopic radical hysterectomy were assessed for eligibility, with 60 patients enrolled and allocated randomly (Fig. 1). Two of these patients were excluded during surgery (1 patient was due to receiving blood transfusion during surgery and another one was due to the conversion to abdominal radical hysterectomy). Data of patients screened but not finally enrolled were not collected. Thus, 29 patients in the TIVA group and 29 patients in the SEVO group were finally evaluated.

3.2. Demographics and surgical details

Patient characteristics are presented in Table 1. The 2 groups were comparable in terms of age, height, weight, ASA status, the International Federation of Gynecology and Obstetrics stage of tumor, and the histological types of tumor. The intraoperative

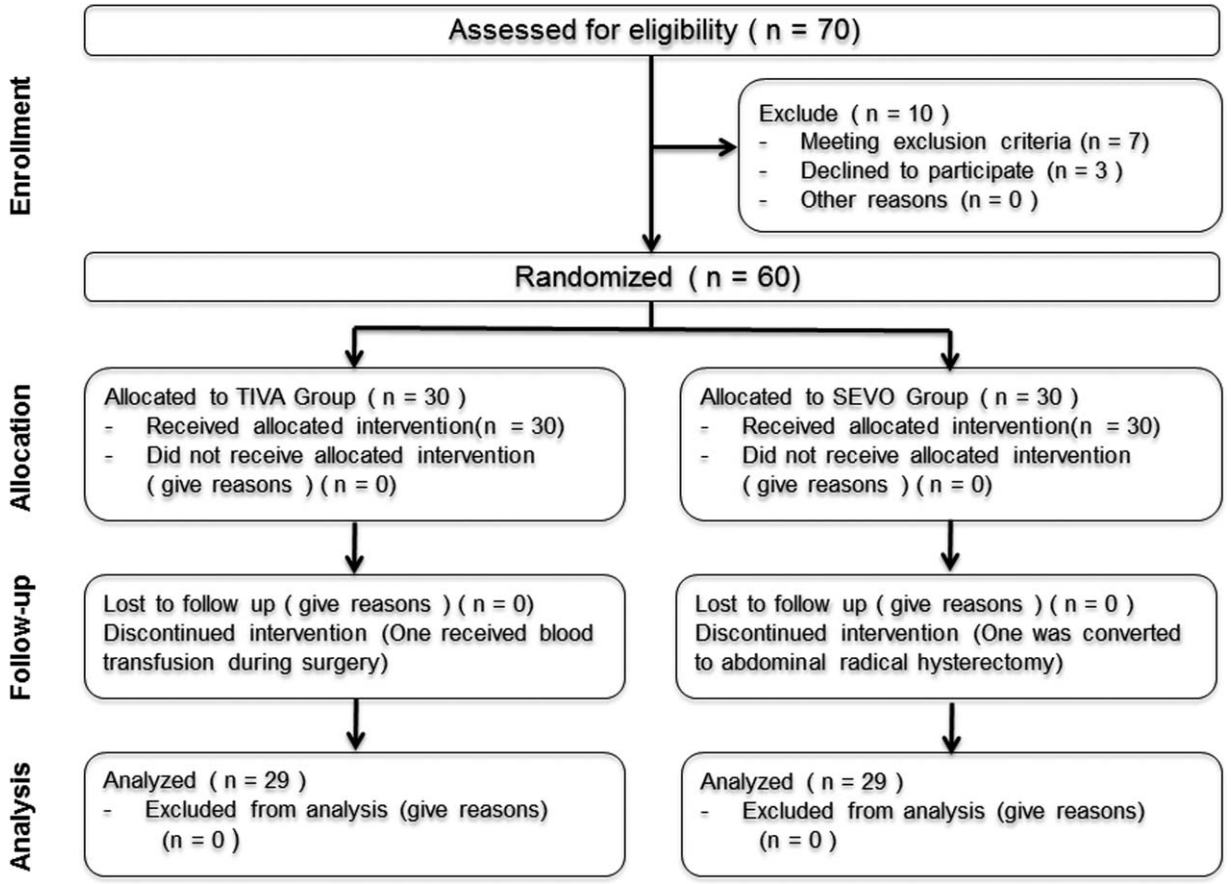

Figure 1. Patient flow diagram (according to the CONSORT chart). SEVO = sevoflurane induction and maintenance, TIVA = propofol induction and maintenance.

parameters were not different, including the operation time, blood loss, crystalloid and colloid infused volume, urine volume, and intraoperative complications (e.g., bladder and ureteral injury) (Table 2).

Table 1

Demographic characteristics.

	TIVA group (n = 29)	SEVO group (n = 29)	*P*
Age, y	45.86 ± 10.03	48.31 ± 9.78	0.35
Height, cm	161.62 ± 5.25	162.41 ± 5.62	0.58
Weight, kg	56.49 ± 9.72	54.72 ± 10.61	0.51
ASA status, I/II	19/10	17/12	0.59
FIGO stage, n (%)			
Ia2	7 (24.13)	8 (27.59)	0.76
Ib1	10 (34.48)	9 (31.03)	0.78
Ib2	3 (10.34)	4 (13.79)	0.69
IIa1	5 (17.24)	4 (13.79)	0.72
IIa2	2 (6.89)	3 (10.34)	0.64
IIb	2 (6.89)	1 (3.45)	0.55
Histology, n (%)			
Squamous cell carcinoma	24 (82.76)	22 (75.86)	0.52
Adenocarcinoma	5 (17.24)	7 (24.14)	0.52

Values are presented as mean ± standard deviation or number of patients (%).
ASA = American Society of Anesthesiologists, FIGO = International Federation of Gynecology and Obstetrics, SEVO = sevoflurane induction and maintenance, TIVA = propofol induction and maintenance.

3.3. Lymphocyte subset counts

As shown in Table 3, there were no significant differences concerning the numbers of circulating lymphocyte subsets and the CD4+/CD8+ ratio between groups before anesthesia induction.

The number of CD3+ cells was significantly decreased after surgery at T_1–T_2 in TIVA group and T_1–T_3 in SEVO group compared with the baseline value at T_0. And at T_1–T_2 time points, the CD3+ cells reduced more in SEVO group than in TIVA group. The CD4+ cells were also reduced significantly in both groups after surgery, but recovered to the normal level only in TIVA group at T_4. The CD4+ lymphocyte counts were lower in

Table 2

Surgical details.

	TIVA group (n = 29)	SEVO group (n = 29)	*P*
Operation time, min	204.62 ± 33.22	215 ± 35.68	0.24
Blood loss, mL	285.52 ± 101.38	274.41 ± 105.54	0.68
Crystalloid received, mL	1143 ± 207.57	1191 ± 202.61	0.39
Colloid received, mL	698.34 ± 165.51	667.79 ± 171.82	0.49
Urine volume, mL	662.34 ± 213.50	609.41 ± 183.69	0.32
Intraoperative complications, n (%)	2 (6.90)	2 (6.90)	1.00

Values are presented as mean ± standard deviation or number of patients (%).
SEVO = sevoflurane induction and maintenance, TIVA = propofol induction and maintenance.

Table 3

Perioperative circulating lymphocyte counts.

	T_0	T_1	T_2	T_3	T_4
CD3+ cells, $10^3/\mu L$					
TIVA	1.80 ± 0.41	1.40 ± 0.52*	1.35 ± 0.41**	1.65 ± 0.54	1.73 ± 0.54
SEVO	1.87 ± 0.52	1.05 ± 0.52***,****	0.98 ± 0.52***,****	1.39 ± 0.53**	1.59 ± 0.53
CD4+ cells, $10^3/\mu L$					
TIVA	1.05 ± 0.33	0.82 ± 0.26*	0.81 ± 0.27*	0.79 ± 0.26**	0.96 ± 0.29
SEVO	1.02 ± 0.32	0.62 ± 0.32***,****	0.58 ± 0.27***,****	0.64 ± 0.30**,***	0.79 ± 0.31*,***
CD8+ cells, $10^3/\mu L$					
TIVA	0.69 ± 0.30	0.84 ± 0.29	0.63 ± 0.27	0.79 ± 0.26	0.75 ± 0.30
SEVO	0.69 ± 0.28	0.77 ± 0.27	0.73 ± 0.33	0.73 ± 0.29	0.84 ± 0.31
CD4+/CD8+					
TIVA	1.76 ± 0.66	1.37 ± 0.72	1.18 ± 0.56**	1.19 ± 0.68**	1.70 ± 0.61
SEVO	1.70 ± 0.69	1.16 ± 0.59****	0.91 ± 0.13***,****	0.88 ± 0.11***,****	1.51 ± 0.65
NK cells, $10^3/\mu L$					
TIVA	0.63 ± 0.28	0.44 ± 0.21*	0.45 ± 0.19*	0.49 ± 0.22	0.56 ± 0.27
SEVO	0.61 ± 0.28	0.45 ± 0.21*	0.33 ± 0.19***,****	0.38 ± 0.12**,***	0.53 ± 0.26
B cells, $10^3/\mu L$					
TIVA	0.47 ± 0.18	0.29 ± 0.34**	0.31 ± 0.12*	0.29 ± 0.13**	0.38 ± 0.18
SEVO	0.48 ± 0.18	0.33 ± 0.11**	0.35 ± 0.10**	0.32 ± 0.11****	0.42 ± 0.19

Values are presented as mean ± standard deviation or number of patients (%).

SEVO = sevoflurane induction and maintenance, TIVA = propofol induction and maintenance.

T_0 = 30 min before induction, T_1 = the end of operation, T_2 = 24 h after operation, T_3 = 48 h after operation, T_4 = 72 h after operation.

*$P < 0.05$, **$P < 0.01$, ****$P < 0.001$, compared with T_0.

***$P < 0.05$, compared with the TIVA group.

SEVO group than that of TIVA group by 72 h after surgery (T_4). There were no obvious changes of CD8+ cell counts were detected during this study period in both groups. The CD4+/CD8+ ratio was significantly lower in TIVA group at T_2–T_3 and in SEVO group at T_1–T_3. They all recovered gradually to the physiologic level 72 h after surgery. We also found that the ratio of CD4+/CD8+ was lower at T_2–T_3 in SEVO group than in TIVA group.

The NK cell counts showed a marked decrease at T_1–T_2 in TIVA group and at T_1–T_3 in SEVO group. The SEVO group also showed a statistically lower number of NK cells than TIVA group at 24 h (T_2) and 48 h (T_3) after surgery.

Compared with the preoperative value, the number of B lymphocytes at T_1–T_3 was significantly lower in both groups, but there were no statistically significant differences between groups.

Table 4

Postoperative characteristics.

	TIVA group (n = 29)	SEVO group (n = 29)	*P*
Duration of catheterization, d	4.97 ± 1.72	5.03 ± 1.57	0.87
Hospital stay, d	6.59 ± 1.43	7.17 ± 1.49	0.13
Postoperative complications, n (%)			
Bladder dysfunction	8 (27.59)	9 (31.03)	0.77
Lymphedema	5 (17.24)	5 (17.24)	1.00
Ileus	0	0	NA
Deep vein thrombosis	0	0	NA
Wound infection	0	0	NA
Urinary tract infection	1 (3.45)	3 (10.34)	0.61
Vaginal cuff infection	0	2 (6.89)	0.49
Febrile morbidity	1 (3.45)	2 (6.89)	1.00

Values are presented as mean ± standard deviation or number of patients (%).

NA = not available, SEVO = sevoflurane induction and maintenance, TIVA = propofol induction and maintenance.

3.4. Postoperative characteristics

The postoperative data are shown in Table 4. The duration of catheterization and the hospital stay period were comparable between 2 groups. Similarly, no statistical differences were found between groups regarding bladder dysfunction and lymphedema. There is no patient who experienced severe complications, such as ileus and deep vein thrombosis. Infection was observed in 4 patients of SEVO group, while only in 1 patient of TIVA group. However, the difference was not statistically significant.

4. Discussion

The different effects of inhalational anesthetics and propofol on the perioperative lymphocyte counts and function in patients undergoing cancer surgery have been studied for a long time. For cervical cancer, several studies have reported that the perioperative lymphocyte counts are important prognostic factors for evaluating postoperative complication and predicting relapse.[16–19] Furthermore, Wu et al suggested that pre- and post-treatment lymphopenia might be associated with deceased survival in patients with cervical cancer.[20]

CD4+ and CD8+ T cells are important effector cells of cell-mediated immunity (CMI). The CD4+/CD8+ ratio is considered to have a positive association with the function of CMI.[21] NK cells, as a firstline of defense, play a key role in destroying tumor cells and micrometastasis[22,23]; and NK cell levels have prognostic significance in a range of neoplasms.[24–28] Our results showed that the counts of CD3+, CD4+ T cells, NK cells, and the CD4+/CD8+ ratio were decreased after surgery and significant lower in SEVO group (sevoflurane induction and maintenance). Besides, the indicators in SEVO group recovered later than that in TIVA group (propofol induction and maintenance). B cells are the major cells involved in the creation of antibodies that circulate in blood plasma and lymph, known as humoral immunity. Here, we found that the number of B lymphocytes was significantly lower than preoperative levels, but

there was no statistically significant difference between groups. These data suggested that propofol is less associated with the impairment of cellular immunity function rather than humoral immunity in such patients with cervical cancer.

The mechanism by which propofol provides favorable effects on the immune system than sevoflurane remains elusive. However, several studies have suggested that immune changes occurring perioperatively are primarily as a result of surgical trauma and subsequent neuroendocrine responses.[3] Activation of the hypothalamic–pituitary–adrenal (HPA) axis is the key response to stress and plays a central role in mediating the effect of surgery on the immune system.[29,30] The activation of HPA axis finally induces the release of glucocorticoids such as cortisol which is known to suppress CMI.[31,32] Besides, activation of the sympathetic nervous system during surgery also has a profound effect on the immune system since the immune organs or lymphoid organs are innervated by sympathetic nerve fibers.[33] The subsequent release of catecholamines from the nerve terminals has predominantly immunosuppressive effects.[34] Several studies indicated that inhalational anesthetics were associated with higher serum concentration of catecholamines and cortisol than propofol.[35–37] Moreover, Marana et al[38] showed that the plasma levels of norepinephrine, epinephrine adrenocorticotropic hormone, and cortisol were significantly lower in patients receiving TIVA anesthesia than patients receiving sevoflurane anesthesia in gynecological laparoscopy, suggesting a better inhibitory effect of propofol on HPA axis and sympathetic nervous system. These evidences may provide explanation, at least partially, for our present results.

Despite the indirect effects of propofol and sevoflurane on immunomodulation, they can also directly affect the lymphocyte biological characteristics. It has been reported that propofol could preserve NK activity and enhance cytotoxic T lymphocyte activity.[39,40] Besides, propofol would not alter the oxidative state of peripheral T cells and might attenuate oxidative injury of lymphocytes induced by sevoflurane.[41,42] In addition, studies have shown that sevoflurane could induce apoptosis in peripheral lymphocyte in dose-dependent and time-dependent manners in vitro via increased mitochondrial membrane permeability and caspase-3 activation.[43,44] Clinically, propofol has been shown to preferably promote the helper T cells to differentiate into Th1 cells, which maintains the Th1/Th2 ratio balance and inhibits surgical stress.[11,45] Jia et al[12] found that propofol was superior to sevoflurane in protecting the lymphocyte from apoptosis induced by caspase-3 or apoptosis-inducing factor so that provide a protective effect for circulating lymphocytes in patients undergoing off-pump coronary artery bypass graft surgery. These in vivo and in vitro mechanisms contribute to the immunoprotective effect of propofol on surgical stress that occurs in perioperative period.

In all forms of surgery, oncological and otherwise, perioperative immunosuppression can result in immediate consequences for patients including delayed wound healing and other septic events.[3] Here, we recorded postoperative characteristics including duration of catheterization, hospital stay period, and postoperative complications and found that no statistical difference was found regarding total incidence of postoperative complication. However, there were 4 patients experienced infection-related postoperative complications in SEVO group; while only 1 was observed in TIVA group. Due to the small sample size of our study, we cannot exclude the possibility that patients receiving sevoflurane anesthesia may develop more infection-related complications than that receiving propofol anesthesia after laparoscopic radical hysterectomy for cervical cancer. Another limitation is that we must not disregard the possibility that perioperative immunosuppression could be associated with long-term sequelae such as tumor recurrence, metastasis, and mortality[4,5,46]; however, we did not evaluate actual long-term clinical outcomes of the patients. Therefore, further studies regarding the long-term effects of propofol and sevoflurane on patients with cervical cancer are warranted to provide us with a comprehensive evaluation.

5. Conclusion

The present study finds that laparoscopic radical hysterectomy for cervical cancer is associated with postoperative lymphopenia. In terms of protecting circulating lymphocytes, propofol was superior to sevoflurane. Although further studies are needed, the present study provides helpful suggestions for selecting suitable anesthesia techniques and anesthetics to minimize immunosuppression during perioperative period and reduce potential short-term and long-term adverse consequence to patients with cervical cancer.

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