JBUON 2017; 22(6): 1416-1421
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

A study on cellular immune function of patients treated with radical resection of pulmonary carcinoma with two different methods of anesthesia and analgesia

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Summary

Purpose: *To compare the influence on the immune system of two different methods of anesthesia and analgesia in patients treated with radical resection of pulmonary carcinoma.*

Methods: *Thirty-four patients treated with radical resection of pulmonary carcinoma were randomly divided into two groups (group A and group B, 17 cases in each group). Patients in group A were administered total intravenous anesthesia (TIVA) without inhaled hypnotics and intravenous analgesia while patients in group B were administered TIVA combined with epidural anesthesia and epidural analgesia. We compared changes of the T cells subsets (CD3+, CD4+, CD8+ and CD4+/CD8+ ratio) and the function of natural killer (NK) cells in patients at 4 time points: before anesthesia, immediately after surgery, 24 hrs after surgery and 72 hrs after surgery. Clinical data were also collected.*

Results: *CD8+ in group A and B was significantly increased ($p<0.01$) while the other indexes CD3+, CD4+, CD4+/CD8+ ratio and NK cells) were significantly decreased ($p<0.05$). There was a significant difference in various indexes (except NK cell) before anesthesia and 72 hrs after surgery in group A ($p<0.01$). Various indexes of patients in group B at 72 hrs after surgery were restored to the values before anesthesia ($p>0.05$). We observed a significant difference in CD3+, CD8+ and CD4+/CD8+ indexes in groups A and B patients at 72 hrs after surgery ($p<0.05$).*

Conclusions: *TIVA combined with epidural anesthesia and epidural analgesia demonstrated less interference with the immune system and determine fast recovery in patients with radical resection of pulmonary carcinoma.*

Key words: *immunological function, NK cells, T cells, total intravenous anesthesia (TIVA)*

Introduction

Currently, the influence of anesthesia on immunity is receiving lot of attention from medical investigators. This is mainly because the drugs used for anesthesia act directly on immunocompetent cell. Pulmonary carcinoma can have many clinical signs such as persistent cough, hemoptysis, lung infections associated with parapneumonic pleurisy [1] and is associated with immune deficiency, which is more severe in iatrogenic autoimmune disorders [2] or patients with comorbidities such as associated severe infection [3].

Besides, anesthesia can be used to adjust the immune system through acting on nervous and endocrine systems [4-6]. Body immunity function can be indirectly improved by anesthesia through adjusting stress reaction in the perioperative period [7]. The degree of stress reaction and mechanism for inhibiting stress reaction are different in various types of anesthesia, which implies that immunity in cancer will be influenced by anesthesia methods in varying degrees [8,9]. Researches show that [10-12] for most cancer patients, the

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Received: 12/04/2017; Accepted: 25/09/2017

killing capacity of NK cells in peripheral blood (PB) are distinctively weakened, the total number of T lymphocytes (CD3+) in circulating blood is decreased, the ratio of T helper cells (CD4+) and T suppressor cells (CD8+) is decreased and the ability of T cell to respond to antigenic stimulation is weakened. Cellular immune functions in which are involved the above effector cells are an important part of antitumor immunity [13].

Therefore, the immunity of lung cancer patients could be severely damaged. Focusing on improving the immunologic function of lung cancer patients, we studied the influence of two different methods of anesthesia and analgesia on the cellular immune function in patients treated with radical resection of pulmonary carcinoma, based on comparison of immune parameters in patients treated with TIVA and intravenous analgesia with patients treated with TIVA combined with epidural anesthesia and epidural analgesia.

Methods

Clinical data

Thirty-four patients of Sir Run Run Shaw Hospital treated with radical resection of pulmonary carcinoma from May 2015 to September 2016 were selected. The study patients were aged between 43 and 71 years, without malformation of the spine, with ASA grade I-II, with BMI<30 kg/m^2, without significant immune, endocrinological, renal and cardiovascular problems, without coagulation disorders, without administration of non-steroidal anti-inflammatory drugs (NSAID), hormone-based drugs and immunosuppressive drugs.

The patients were randomly divided into two groups. Group A was given TIVA and intravenous analgesia and group B was given TIVA combined with epidural anesthesia and epidural analgesia. Detailed potential risks of this research had been explained to patients and their families before inclusion in the study. Detailed medical history was obtained from all study participants and informed consent was signed by the patients and their relatives. The study was approved by medical ethics committee of Sir Run Run Shaw Hospital, and was conducted in accordance with Helsinki Declaration of 1975 as revised in 2000 concerning ethical standards on human experimentation.

Research material and experimental apparatus

Pharmaceutic substances: Propofol injection (Deprivan bought from Anhui Tianyi Pharmaceutical Co., Ltd). Hydrochloric ropivacaine injection (Naropin bought from Beijing Kanglilai Medical Co.). Cisatracurium besilate for injection (Jiangsu Hengrui Medical Incorporated Co.). Bleomycin A hydrochloride for injection (YichangRenfu Medical Co., Ltd). Midazolam injection (Zhejiang Jiuxu Pharmaceutical Co., Ltd). Sufentanyl Citrate injection (Germany IDT Biologika GmbH).

Consumables and reagents: Disposable puncture bag for anesthesia (Shanghai Pudong Jinhuan Medical Supplies Ltd), postoperation analgesia infusion pump (Jiangsu Huaxia Medical Equipment Co., Ltd), binary channels target-controlled infusion (Guangzhou Tiancheng Medical Technology Incorporated Co.).

Instruments used: Anesthesia workstation (Drager Medical AG & Co. KgaA). Bispectral index (BIS) detector (USA), flow-cytometer (The Netherlands, CytoBuoy Co.), detection kit for lymphocyte subpopulations (Bicolor fluorescent antibody in detection kit was monoclonal antibody of mouse anti-human marked by fluorescein isothiocyanate and phycoerythirin, BD Diagnostics), high-speed refrigerated centrifuge (Beijing ShidaiBeili Centrifuge Co., Ltd), laminar flow clean bench (Shandong BokeBiobase Co., Ltd), ultra-low temperature freezer (Shanghai Tianfeng Industrial Co., Ltd).

Research methods

Anesthesia method

After 5 min from the time that all patients entered in the laboratory, blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) and peripheral oxyhemoglobin saturation (SpO2) were measured and set as base values.

Group A: After venous transfusion access was prepared, general anesthesia induction was administered (500 mcg/kg iv. midazolam, remifentanyl with target concentration of 6 ng/ml; propofol with target concentration of 6 μg/ml; cisatracurium of 0.1-0.15 mg/kg). When the patient was intubated with double-lumen tube, the anesthesia machine was connected to provide mechanical ventilation. Tidal volume of double lung ventilation was set at 8-10 ml/kg and respiratory rate was 12-13 times/min. When the tube was intubated into the chest, it was changed to one-lung ventilation. During the operation, propofol and remifentanyl were administered through controlled infusion (target concentration was controlled at 3-6 μg/ml) and cisatracuriumin dose of 0.05 mg/kg was discontinuously injected to maintain muscular flaccidity. Meanwhile, 40 mg parecoxib was used as associate analgesia and 0.2 mg palonosetron was used to prevent emesis.

Group B: When patients entered laboratory and their intravenous line was established, epidural puncture was performed at T7-T8. When there was no adverse symptom of total spin anesthesia, general anesthesia was administered with the same method as in group A. Ropivacaine 0.375% and 3-5 ml was given at epidural before surgery, which was repeated every 30 min for 1-2 times during the operation. Propofol and remifentanyl were administered through intravenous target controlled infusion and cisatracurium was discontinuously injected while other drugs used in surgery, anesthesia depth and haemodynamics index were the same as in group A. Before the chest closing phase (around 30 min before finishing surgery), ropivacaine was added in the epidural line for the last time as load capacity. Then, analgesia pump was connected to epidural line (dose 300 ml, sufentanyl 3 μg/kg, ropivacaine 0.2%, flow rate 4 ml/h).

Monitored value and dosage record

HR, BP, MAP and SpO2 were measured every min during surgery in both groups. Surgery time and dosage of propofol, remifentanyl and ropivacaine were recorded (Table 1). Analgesic effect was recorded by VAS evaluation on a scale from 0 to 10 points (Figure 1). Adverse reactions such as dizziness, headache, nausea and vomiting and hypotension caused by analgesia pump were recorded.

Blood collection and timing

Venous blood of 34 patients with central venous catheter was taken from the right vena jugularis interna or right subclavian vein. Two ml of blood were extracted each time and ethylene diaminetetraacetic acid (EDTA) sylvite was used as anticoagulant. After extraction, the blood specimens were immediately sent for testing. Time points for collecting blood were t 0 (before aneathesia), t1 (after surgery), t2 (24 hrs after surgery) and t3 (72 hrs after surgery).

Laboratory methodology

Flow-cytometer (FCM) and the matching detection kit of lymphocyte subpopulation were used. Twenty µl of corresponding monoclonal antibodies (MAb) were added to flow test tube, and then 100 µl blood with heparin anticoagulation were added to be tested. After mixing, the tube was left for 30 min at room temperature to allow reaction to produce. Two mL of hemolysin was added twice. After mixing, it was kept in the dark for 5 min at room temperature and centrifuged at 1200 rpm for 5 min. Afterwards, the supernatant was discarded and PBS mixed with stirrer was added. Then, the mixture was centrifuged again at 1200 rpm for 5 min and the supernatant was discarded. Three hundred µl of stationary liquid was added to it and then stirred again. Flow cytometry analysis followed and fluorescence compensation was conducted after light path and flow path were corrected. Finally, the sample was tested.

Statistics

Statistical analysis was performed by SPSS19.0 software and measurement data was expressed by mean ± standard deviation. One-way analysis of variance (ANOVA) of repeated data measuring was used for intra-group and inter-group comparisons. A p value <0.05 showed statistical significance.

Results

Comparison of clinical data between groups

As shown in Table 1, no significant differences between patients in terms of age, gender, BMI, op-

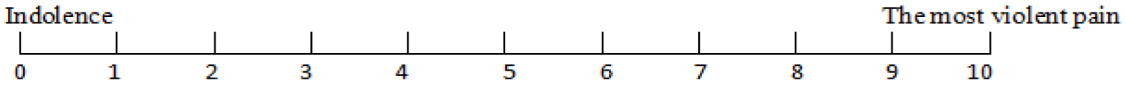

Figure 1. VAS evaluation scale.

Table 1. Comparison of clinical data between groups

Groups	*Age (years)*	*Gender (Male /Female)*	*BMI (kg/m²)*	*Anesthesia time (min)*	*Dosage of propofol (mg)*	*Dosage of ropivacaine (mg)*	*Dosage of remifentanyl (mg)*
Group A	56±6[1]	13/7	27±2.3[1]	173±45[1]	983±145[1]	-	1.8±0.5[1]
Group B	59±7[1]	12/8	25±2.4[1]	165±36[1]	877±136[1]	42.88±11.02[1]	1.4±0.6[1]*

BMI: body mass index, [1]mean±SD, *p<0.05.

Table 2. Comparison of haemodynamics of perioperative period and change of BIS (Bispectral index) value (mean±SD)

Group	*Time*	*HR (bpm)*	*SBP (mmHg)*	*DBP (mmHg)*	*MAP (mmHg)*	*SpO2 (%)*	*BIS*
A	t1	77±9	125±17	79±11	95±14	97±2	96±3
	t2	83±10	129±16	79±13	89±15	98±1	46±3
	t3	84±12	127±14	77±11	86±13	98±2	54±4
	t4	76±9	123±12	75±10	91±13	98±1	48±4
	t5	74±8	115±13	72±10	87±11	98±1	59±6
	t6	78±9	117±12	74±10	88±13	97±1	84±4
B	t1	79±10	127±16	78±13	94±14	96±2	96±4
	t2	81±11	127±18	79±11	85±14	98±2	44±3
	t3	82±11	115±15	75±11	81±12	98±1	51±3
	t4	75±10	119±13	73±13	85±14	98±2	49±4
	t5	72±8	117±14	72±11	79±11	98±1	57±6
	t6	72±9	115±12	73±10	81±12	98±2	82±5

t1: before surgery; t2: anesthesia begins, tube intubated; t3: surgery begins, skin cut; t4: entering chest; t5: at the end of surgery; t6: anesthesia is over, tube drawn.

erative time and dosage of propofol and ropivacaine were recorded (p>0.05). However, there was a significant difference between patients in the two groups in terms of dosage of remifentanyl (p<0.05).

Haemodynamics of perioperative period and change of bispectral index value

As shown in Table 2, no significant differences in the two groups in terms of HR, BP, MAP, SpO2 and BIS value of different time points were noticed (p>0.05).

At 24 hrs, the analgesic effect was significantly lower in group B than in group A (p<0.01) (Table 3).

T cells and NK cells of patients in two groups

Table 4 shows an increase in CD8+ in patients of the two groups after surgery with the highest level 24 hrs after surgery (p<0.01). Other cell characteristics decreased significantly after surgery (p<0.05). CD3+ and CD4+ fell to their lowest level right after the surgery (p<0.01), and increased at 24 hrs after surgery. CD4+/CD8+ ratio and NK cells of the two groups fell to their lowest level at 24 hrs after surgery. Significant differences (p<0.05) were noticed for all indexes of group A except NK cells before surgery and 72 hrs after surgery. All indexes of group B restored almost to the level before anesthesia 72 hrs after surgery (p>0.05). However, significant differences were noted for CD3+, CD8+ and CD4+/CD8+ in patients of the two groups 72 hrs after surgery (p<0.05).

Discussion

Tumorigenesis and tumor progression is related to the decrease of the immunologic functions [14]. Tumor cells can secret substances to suppress immunological competence while cellular immunity play an important role in antitumor immunological effects [15,16]. T lymphocytes are not only effector cells of cellular immunity but also immunoregulators, whose subgroup changes reflect the cellular immunity status [17-19]. CD3+ cells are expressed on the surface of all mature T cells in order to assist T cell receptor (TCR) to identify epitopes of the major histocompatibility complex (MHC) on antigen-presenting cells (APC) [20]. The TCR ability to identify MHC is influenced by the lowered CD3+ cell count, thus negatively affects the immunologic function [21]. CD4+ cells are expressed on the surface of T helper cell (Th) of CD8+ cytotoxic T cell to kill tumor cells by secreting a large amount of cytokines. Besides, immunologic memory T cells can kill tumor cell directly [22,23]. CD8+ cells are expressed on the surface of suppressor T cells (Ts) and cytotoxic T cells (CTL) that inhibit antibody synthesis and secretion and T cell proliferation [24]. Changes of Th/Ts ratio reflect the changes of immunological function. CD4+ and CD8+ cells provide intercoordination and inter-constraint and adjust the immune response together [24,25], thus, unbalanced ratio of CD4+ and CD8+ would result in immune dysfunction. NK cells play an important role in controlling tumor growth and preventing or reducing blood dissemination [26-28]. T lymphocyte subpopulations and NK cells are responsible for immunological surveillance and play a significant role in activating inflammatory reaction, recognizing and killing tumor cells and decreasing postoperative tumor metastasis [29]. The results of the present study showed that CD3+, CD4+, CD4+/CD8+ and NK cells in groups A and

Table 3. VAS evaluation of patients of two groups 24 hrs after surgery

Groups	*<3 points*	*3-4 points*	*4-6 points*	*>6 points*	*Total*
Group A	7	4	6	0	17
Group B	12	5	0	0	17

Table 4. Comparison of change of T cell subsets and NK cells (mean±SD)

Time	*Groups*	*CD3+*	*CD4+*	*CD8+*	*CD4+/CD8+*	*NK cell*
t0	Group A	56.03±8.33	35.02±4.96	28.02±4.27	1.31±0.45	13.70±4.02
	Group B	58.45±8.63	33.11±6.21	27.56±5.11	1.26±0.42	14.03±4.58
t1	Group A	41.91±8.79#	23.18±5.09#	31.78±5.52*	0.81±0.34#	12.13±3.69
	Group B	40.14±8.64#	24.41±4.13#	31.01±7.43	0.86±0.35#	11.27±3.63*
t2	Group A	45.61±7.84#	26.47±5.41#	35.26±6.09#	0.77±0.27#	10.11±3.08#
	Group B	48.48±7.46#	26.63±4.67#	33.72±7.87#	0.84±0.22#	10.62±3.92#
t3	Group A	46.93±6.11#	28.96±5.50#	33.90±4.93#	1.01±0.30#	12.40±3.05
	Group B	54.81±6.87‡	31.27±6.03	27.63±5.68‡	1.17±0.28‡	13.49±4.42

Different groups were compared to t0, *p<0.05, #p<0.01. Intra-group and group A were compared, ‡p<0.05.

B 24 hrs after surgery were lowered compared to those before anesthesia and there was no significant difference between groups. In our opinion, the results showed no significant difference between groups due to enhanced stress reaction, long post-intervention time and large anesthesia dosage, therefore no advantage of epidural anesthesia was shown. However, immunological function recovered more quickly in group B patients than in those in group A, when the above factors were gradually eliminated. Moreover, CD3+, CD4+, CD4+/CD8+ and NK cell of group B patients could almost restore to the level before anesthesia 72 hrs after surgery ($p<0.05$).

Different medications are used for different anesthesia and analgesia methods. In this study all patients were administered controlled infusion with propofol combined with remifentanyl and sufentanyl for analgesia after surgery. Ropivacaine was used in group B for epidural anesthesia. Propofol can be used for anti-inflammatory effects and promoting protective immunity. Clinically, propofol was more effective than inhaled anesthetic in the reduction of immunosuppression caused by surgical stress [30,31]. This can be due to enhancement of transcription factor activity of Th cells [32]. Some studies on patients treated with radical resection of pulmonary carcinoma showed that propofol combined with remifentanyl with target controlled infusion can stabilize their haemodynamics and effectively reduce their stress reaction and immunosuppressive effects [33-35]. Remifentanyl has shown a quick result but short effective time [36], thus it is controversial whether or not it would have a negative effect on immunity in postoperative analgesia [37,38]. Some authors used 5 ml 1% lidocaine epidural infusion to reduce stress reaction in the perioperative period [39], in order to reduce the inhibiting effect of lidocaine to T lymphocytes. For patients in group B, ropivacaine 0.375% was used in the epidural line for analgesia and its postoperative VAS evaluation was relatively low, meaning that the analgesic effect was good, not to neglect its benefits to immunologic function recovery.

In conclusion, for quick immunologic function recovery, a lung cancer patient with severe immunodeficiency can be treated with TIVA combined with epidural anesthesia and epidural analgesia.

Acknowledgements

This work was supported by Medicine Research Program of Health and Family Planning Commission of Zhejiang Province, China. Award Number: 2016KYB144.

Conflict of interests

The authors declare no conflict of interests.

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