Effect of anesthetic methods on postoperative $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ in patients with lung cancer undergoing radical operation

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Abstract. Effects of anesthesia methods on immune function in patients with lung cancer undergoing radical operation were investigated. A total of 122 patients undergoing radical resection of lung cancer who were treated in Zhejiang Cancer Hospital from September 2013 to April 2016 were randomly divided into the combined anesthesia group and the intravenous anesthesia group, with 61 cases in each group. The patients in the combined anesthesia group were given intravenous combined epidural anesthesia. Patients in the intravenous anesthesia group were given intravenous anesthesia. The change of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at time-point T0 (before anesthesia), T1 (the time of anesthesia), T2 (after operation), T3 (24 h after operation), T4 (72 h after operation) were compared between the two groups. The levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T1, T2, T3 and T4 in the combined anesthesia group were higher than that in the intravenous anesthesia group ($P<0.05$). After starting anesthesia, the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ began to decrease in both groups. The levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T2 and T1 were lower than those at T0 ($P<0.05$). The levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T2 were lower than T1 ($P<0.05$). After T3, the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ began to increase in both groups. The levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T3 and T4 were higher in both groups than those at T2 and T1 ($P<0.05$), and the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T4 were higher in both groups than those at T3, but the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ at T3 and T4 were lower than those at T0 ($P<0.05$). Intravenous combined epidural anesthesia can maintain a relatively stable immune function compared with simple intravenous anesthesia patients.

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Introduction

Lung cancer is a malignant tumor with the highest mortality rate in the world, with a prevalence of approximately 2-3:1 in men and women (1). With industrial development, the incidence and mortality rate of lung cancer are still rising (2). Radical operation is the main treatment of lung cancer and is the only way to cure lung cancer at present. However, it causes severe trauma to the body and intense stimulation to the organ, which can easily lead to a strong stress response in the body and cause a decrease in immune function. While the autoimmune function of patients with lung cancer is lower than healthy people, which is one of the important factors leading to the not ideal results in radical resection of lung cancer treatment (3-5).

Anesthesia is one of the most important auxiliary means of surgery. Appropriate anesthesia has a decisive significance in maintaining vital signs of patients and in helping perioperative patients (6). However, the current use of various narcotic drugs is not ideal, in order to improve this deficiency, combined anesthesia came into being (7). Combined anesthesia, also known as balanced anesthesia, is the combination of two or more narcotic drugs or anesthesia method in order to improve perioperative analgesia effect and surgical conditions (8). Combined general epidural anesthesia is currently the main method of combined anesthesia, it can reduce the use of anesthetic drugs in surgery, can improve the analgesic effect, reduce side effects and adverse reactions, improve surgical safety, and also eliminate the fear and tension of patients, reduce stress response, improve patient immune function (9,10).

The purpose of this study was to investigate the effects of intravenous combined epidural anesthesia on patients with lung cancer undergoing radical surgery and to investigate the effects of intravenous combined epidural anesthesia on immune function in patients with lung cancer by dynamically monitoring the changes of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$.

Materials and methods

Patients. A total of 122 patients undergoing radical resection of lung cancer treated in Zhejiang Cancer Hospital (Hangzhou, China) from September 2013 to April 2016 were randomly divided into two groups: Combined anesthesia group and intravenous anesthesia group, 61 cases in each group. Patients in the combined anesthesia group received intravenous combined epidural anesthesia. Patients in the intravenous anesthesia group were given intravenous anesthesia alone. Inclusion criteria were: Patients in Zhejiang Cancer Hospital pathology department; no past history of tumor, diagnosed and received a series of tests and treatment in Zhejiang Cancer Hospital, willing to cooperate with medical staff in Zhejiang Cancer Hospital. Exclusion criteria were: Patients with other cardiovascular and cerebrovascular diseases, patients with other gastrointestinal diseases, patients who were transferred midway through the course of treatment or taking antibiotics not prescribed by Zhejiang Cancer Hospital or those who had been treated in a non-hospital setting for rehabilitation. This study was approved by the Zhejiang Cancer Hospital Ethics Committee. Written informed consents were collected and signed by the patients.

Treatment method. Intravenous anesthesia group was given simple intravenous anesthesia. Combined anesthesia group was given intravenous combined epidural anesthesia. All patients were given intramuscular injection of midazolam (0.05 mg/kg, H10980025; Jiangsu Enhua Pharmaceutical Co., Ltd., Xuzhou, China) and atropine (0.5 mg/patient, H44024022; Guangdong Nanguo Pharmaceutical Co., Ltd., Zhanjiang, China) for 30 min before entering the operating room, and GT6800-12 monitor (Hunan Yimin Sunshine Technology Co., Ltd., Hunan, China) was used for monitoring of vital signs and timely establishment of venous fluid path. Anesthesia was induced by intravenous injection of fentanyl (2 μg/kg, H42022076; Yichang Renfu Pharmaceutical Co., Ltd., Yichang, China) and propofol (2 mg/kg, H20163040; Xi'an Libang Pharmaceutical Co., Ltd.). After the patient lost consciousness, atracurium (0.5 mg/kg, H20090202; Zhejiang Xianju Pharmaceutical Co., Ltd., Zhejiang, China) was given until the patient's vital signs became stable and then tracheal intubation was performed.

Intravenous anesthesia: Intravenous target-controlled infusion of remifentanil (0.02 μg/kg/min, H20143314; Yichang Renfu Pharmaceutical Co., Ltd.) combined with propofol (0.05 μg/kg/min) maintaining anesthesia until 10 min prior to surgery with intermittent administration of atracurium (0.1 mg/kg).

Intravenous combined epidural anesthesia: After endotracheal intubation, epidural puncture was performed in the waist 5 to the waist 6 or waist 6 to the waist 7 levels of local administration of 1% lidocaine (5 ml, H41023668; Sui Cheng Pharmaceutical Co., Ltd.). Intraoperative target-controlled infusion of propofol (0.05 μg/kg/min) was performed to maintain anesthesia while administering 0.375% ropivacaine every 30 min (5 ml, H20113381; Guangdong Jiabo Pharmaceutical Co., Ltd., Guangzhou, China) till 10 min before the end of the surgery, and atracurium was given intermittently (0.1 mg/kg).

Observation indicators. Peripheral blood samples were collected before anesthesia (T0), immediately after anesthesia (T1), after operation (T2), 24 h after operation (T3) and 72 h after operation (T4), and $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ levels were detected at all 5 time-points using a MACSQuant flow cytometer from Gene Tech Co., Ltd. (Hong Kong, China).

Statistical analysis. Statistical methods: SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Enumeration data were expressed as n (%) and were examined by χ^2 test. Measurement data were expressed as mean ± SD. Comparison between multiple groups was done using One-way ANOVA test followed by post hoc test (Least Significant Difference). $P<0.05$ for the difference was considered statistically significant.

Results

General information. There were 122 patients in line with the inclusion criteria, 61 cases in intravenous anesthesia group. There were 36 male and 25 female patients, mean age 53.5±6.4 years, 61 cases of joint anesthesia group, including 38 males and 23 females, mean age 54.3±6.6 years (Table I). There was no significant difference in gender proportion and average age between the two groups ($P>0.05$). Body mass index, operation time and preoperative life parameters of two groups of patients showed no difference ($P>0.05$).

Analysis of T0, T1, T2, T3 and T4 $CD3^+$ levels in the groups. There was no difference in $CD3^+$ level at T0 between the two groups ($P>0.05$). $CD3^+$ levels at T1, T2, T3 and T4 were significantly higher in the combined anesthesia group than those in the intravenous anesthesia group ($P<0.05$). The level of $CD3^+$ at T2 and T1 was lower than that at T0 ($P<0.05$), and the level of $CD3^+$ at T2 was lower than that at T1 ($P<0.05$). After T3, the level of $CD3^+$ increased in both groups; the levels of $CD3^+$ at T3 and T4 were higher in both groups than those in T2 and T1 ($P<0.05$). The levels of $CD3^+$ at T4 were higher than those at T3 in both groups ($P<0.05$). All $CD3^+$ levels at T3 and T4 were lower than T0 in both groups ($P<0.05$) (Table II).

Analysis of $CD4^+$ levels in two groups at T0, T1, T2, T3 and T4. There was no significant difference in $CD4^+$ level between two groups at T0 ($P>0.05$). $CD4^+$ levels at T1, T2, T3 and T4 were significantly higher in the combined anesthesia group than those in the intravenous anesthesia group ($P<0.05$). After the start of anesthesia, $CD4^+$ levels of both groups started to decrease. $CD4^+$ levels at T2 and T1 were lower than those at T0 ($P<0.05$), and $CD4^+$ levels at T2 were lower than those at T1 ($P<0.05$). After T3, the levels of $CD4^+$ in both groups began to increase ($P<0.05$); the levels of $CD4^+$ in both groups at T3 and T4 were higher than those at T2 and T1 ($P<0.05$). The levels of $CD4^+$ at T4 were higher in both groups than those at T3 ($P<0.05$), but the level of $CD4^+$ at T3 and T4 were lower than those at T0 ($P<0.05$) (Table III).

Analysis of $CD4^+CD25^+$ levels in two groups at T0, T1, T2, T3 and T4. There was no significant difference in $CD4^+CD25^+$ level between the two groups at T0 ($P>0.05$). $CD4^+CD25^+$ levels at T1, T2, T3 and T4 were significantly higher in the

Table I. Clinical data comparison of two groups.

Items	Intravenous anesthesia	Combined anesthesia	t/χ^2 value	P-value
No. of patients	61	61		
Sex			0.371	0.711
Male	36	38		
Female	25	23		
Age (years)	53.5±6.4	54.3±6.6	0.680	0.498
BMI (kg/m^2)	24.82±10.13	25.17±10.46	0.188	0.851
Operation time (min)	81.13±12.56	81.75±12.72	0.271	0.787
Preoperative diastolic blood pressure (mmHg)	78.25±7.33	78.36±7.45	0.082	0.934
Preoperative systolic blood pressure (mmHg)	133.46±14.12	133.17±13.69	0.115	0.909
Preoperative heart rate (beats/min)	78.29±9.17	78.48±9.36	0.113	0.910

Table II. $CD3^+$ level analysis at T0, T1, T2, T3 and T4 (%).

Items	Intravenous anesthesia	Combined anesthesia	t-value	P-value
No. of patients	61	61		
T0[a]	62.03±10.15	61.79±10.16	0.131	0.896
T1[b]	50.13±8.14	56.58±8.38	4.312	<0.001
T2[c]	46.14±6.94	53.28±7.48	5.465	<0.001
T3[d]	48.25±8.15	57.97±8.67	6.380	<0.001
T4[e]	52.24±8.13	61.59±8.48	6.216	<0.001

The levels of $CD3^+$ at T1[b], T2[c], T3[d], T4[e] in both groups were significantly lower than those in T0[a] (P<0.05). The levels of $CD3^+$ at T2[c] were significantly lower than those at T1[b] (P<0.05). The levels of $CD3^+$ at T3[d] and T4[e] in both groups were higher than those at T1[b], T2[c]; the levels of $CD3^+$ at T4[e] in both groups were higher than those at T3[d] (P<0.05).

Table III. $CD4^+$ level analysis at T0, T1, T2, T3 and T4 (%).

Items	Intravenous anesthesia	Combined anesthesia	t-value	P-value
No. of patients	61	61		
T0[a]	39.12±7.04	39.17±7.01	0.039	0.969
T1[b]	30.03±6.19	34.22±6.73	3.579	<0.001
T2[c]	26.13±6.32	31.82±6.91	4.746	<0.001
T3[d]	30.97±5.12	35.88±5.38	5.163	<0.001
T4[e]	34.01±4.84	37.69±5.13	4.075	<0.001

The levels of $CD4^+$ at T1[b], T2[c], T3[d], T4[e] in both groups were significantly lower than those in T0[a] (P<0.05). The levels of $CD4^+$ at T2[c] were significantly lower than those at T1[b] (P<0.05). The levels of $CD4^+$ at T3[d] and T4[e] in both groups were higher than those at T1[b], T2[c]; the levels of $CD4^+$ at T4[e] in both groups were higher than those at T3[d] (P<0.05).

combined anesthesia group than those in the intravenous anesthesia group (P<0.05). After the start of anesthesia,

Table IV. $CD4^+CD25^+$ level analysis at T0, T1, T2, T3 and T4 (%).

Items	Intravenous anesthesia	Combined anesthesia	t-value	P-value
No. of patients	61	61		
T0[a]	7.83±1.25	7.79±1.17	0.183	0.856
T1[b]	5.40±1.46	6.24±1.91	2.729	0.007
T2[c]	4.77±0.75	5.73±0.62	7.705	<0.001
T3[d]	5.25±0.84	6.21±1.01	5.708	<0.001
T4[e]	5.83±1.02	7.22±1.13	7.132	<0.001

The levels of $CD4^+CD25^+$ at T1[b], T2[c] in both groups were significantly lower than those in T0[a] (P<0.05). The levels of $CD4^+CD25^+$ at T2[c] were significantly lower than those at T1[b] (P<0.05). The levels of $CD4^+CD25^+$ at T3[d] and T4[e] in both groups were higher than those at T1[b], T2[c]; the levels of $CD4^+CD25^+$ at T4[e] in both groups were higher than those at T3[d] (P<0.05).

$CD4^+CD25^+$ levels of both groups started to decrease, and $CD4^+CD25^+$ levels at T2 and T1 were lower than those at T0 (P<0.05), and $CD4^+CD25^+$ levels at T2 were lower than those at T1 (P<0.05). After T3, the levels of $CD4^+CD25^+$ in both groups began to increase (P<0.05); the levels of $CD4^+CD25^+$ in both groups at T3 and T4 were higher than those at T2 and T1 (P<0.05). The levels of $CD4^+CD25^+$ at T4 were higher in both groups than those at T3 (P<0.05), but the level of $CD4^+CD25^+$ at T3 and T4 were lower than those at T0 (P<0.05) (Table IV). Changes of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ are shown in Figs. 1-3.

Discussion

Different methods of surgery and anesthesia often cause different degrees of stress response in the patients. Due to individual differences, patients also experience different ranges of stress response (11). Stress response within a certain range can enhance the body's immune function, stimulate cell

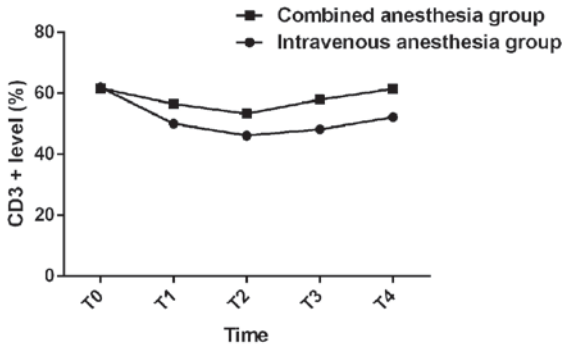

Figure 1. Analysis of T0, T1, T2, T3 and T4 $CD3^+$ levels in two groups. There was no difference in $CD3^+$ level at T0 in the two groups (P>0.05). $CD3^+$ levels at T1, T2, T3 and T4 were significantly higher in the combined anesthesia group than those in the intravenous anesthesia group (P<0.05). The level of $CD3^+$ at T2 and T1 was lower than that at T0 (P<0.05), and the level of $CD3^+$ at T2 was lower than that at T1 (P<0.05). After T3, the level of $CD3^+$ increased in both groups; the levels of $CD3^+$ at T3 and T4 were higher in both groups than those in T2 and T1 (P<0.05). The levels of $CD3^+$ at T4 were higher than those at T3 in both groups (P<0.05). All $CD3^+$ levels at T3 and T4 were lower than T0 in both groups (P<0.05).

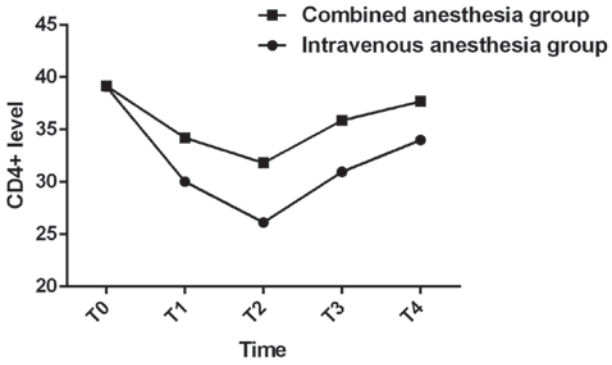

Figure 2. Analysis of $CD4^+$ levels in two groups at T0, T1, T2, T3 and T4. There was no significant difference in $CD4^+$ level between two groups at T0 (P>0.05). $CD4^+$ levels at T1, T2, T3 and T4 were significantly higher in the combined anesthesia group than those in the intravenous anesthesia group (P<0.05). After the start of anesthesia, $CD4^+$ levels of both groups started to decrease. $CD4^+$ levels at T2 and T1 were lower than those at T0 (P<0.05), and $CD4^+$ levels at T2 were lower than those at T1 (P<0.05). After T3, the levels of $CD4^+$ in both groups began to increase (P<0.05); the levels of $CD4^+$ in both groups at T3 and T4 were higher than those at T2 and T1 (P<0.05). The levels of $CD4^+$ at T4 were higher in both groups than those at T3 (P<0.05), but the level of $CD4^+$ at T3 and T4 were lower than those at T0 (P<0.05).

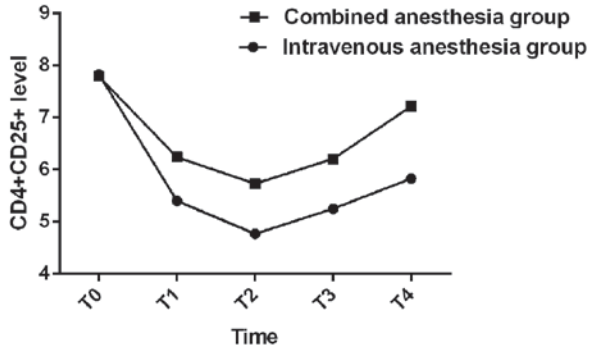

Figure 3. Analysis of $CD4^+CD25^+$ levels in two groups at T0, T1, T2, T3 and T4. There was no significant difference in $CD4^+CD25^+$ level in the two groups at T0 (P>0.05); $CD4^+CD25^+$ levels at T1, T2, T3 and T4 were significantly higher in the combined anesthesia group than those in the intravenous anesthesia group (P<0.05). After the start of anesthesia, $CD4^+CD25^+$ levels of both groups started to decrease, and $CD4^+CD25^+$ levels at T2 and T1 were lower than those at T0 (P<0.05), and $CD4^+CD25^+$ levels at T2 were lower than those at T1 (P<0.05). After T3, the levels of $CD4^+CD25^+$ in both groups began to increase (P<0.05); the levels of $CD4^+CD25^+$ in both groups at T3 and T4 were higher than those at T2 and T1 (P<0.05). The levels of $CD4^+CD25^+$ at T4 were higher in both groups than those at T3 (P<0.05), but the level of $CD4^+CD25^+$ at T3 and T4 were lower than those at T0 (P<0.05).

metabolism to speed up and improve the body's resistance to external stimuli, but the stress response exceeding the body's limit will seriously hinder the treatment of patients with prognosis, and it will inhibit immune function of the body, causing cell and organ damage in patients (12,13). Cellular immunity plays an important role in the anti-inflammatory and antitumor responses of the body (14). This study explored the effects of different anesthesia on the cellular immune function in patients undergoing radical resection of lung cancer, in order to provide reference for the choice of anesthesia in surgical treatment opinion.

$CD3^+$ is a mature T lymphocyte, which can prompt the body's cellular immune function status; $CD4^+$ is a helper T cells, which is the most important hub to regulate the immune response; $CD4^+CD25^+$ is a subset of T cells, which plays an important role in the body inflammation and immune response (15,16). The results of this study showed that the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ in the two groups were lower than those before the operation, but the levels of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ in the patients receiving intravenous combined epidural anesthesia were significantly higher than those in the simple intravenous anesthesia. After surgery, two groups of patients with varying degrees of $CD3^+$, $CD4^+$ and $CD4^+CD25^+$ levels were restored. Patients receiving intravenous composite epidural anesthesia were significantly better than those who received intravenous anesthesia alone, indicating that patients receiving intravenous composite epidural anesthesia had more stable intraoperative immunologic function and better postoperative immune function recovery. This may be related to intravenous compound epidural anesthesia on the inhibition of the stability of the autonomic nervous system; epidural anesthesia can change autonomic nerve function (17), and stabilize the autonomic nervous system, improve the level of peripheral neurotransmitters, effectively improve the anesthesia of T Lymphocyte inhibition, maintain patients with perioperative cellular immune function stability and balance (18). Ropivacaine is an anesthetic with small fat-soluble and relatively diminished absolute efficacy. It blocks motor and sensory nerves independently during maintenance anesthesia and relieves stress stimulation of body anesthesia, surgery and postoperative pain (19). Some studies (20) showed that intraoperative continuous maintenance of ropivacaine in patients with T lymphocyte response was significantly higher. Chen *et al* (21) in the study also showed that the general anesthesia combined with epidural anesthesia can effectively improve the patient's immune function. Kun *et al* (22) also reported in the study that systemic combined epidural anesthesia has a weaker NK cell suppressive effect in gastric cancer surgery compared with pure general anesthesia, which helps to maintain perioperative immune function in patients. Their findings are similar to ours, but because of the short duration of our study, we were unable to assess the longer duration of immune function and adverse

events. Therefore, the findings and conclusions of this study need more research and data for confirmation.

In conclusion, intravenous combined epidural anesthesia can maintain a relatively stable immune function of patients compared to simple intravenous anesthesia.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SF wrote the manuscript and treated the patients. PSQ detected $CD3^+$, $CD4^+$ levels. SNC treated the patients and helped with detection of $CD4^+CD25^+$ levels. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhejiang Cancer Hospital (Hangzhou, China). Patients who participated in this research, signed the informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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