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Effects of Different Anesthesia Methods on Infection, Immune Function and Stress Response of Elderly Patients After Radical Gastrectomy

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Abstract

AIM: To evaluate the effects of general anesthesia and general anesthesia combined with epidural anesthesia on the infection, immune function and stress response of elderly patients after radical gastrectomy.

MATERIALS AND METHODS: A total of 118 elderly patients undergoing radical gastrectomy from October 2016 to November 2019 were randomly divided into control group (n=59) and experimental group (n=59), and treated with general anesthesia and general anesthesia combined with epidural anesthesia, respectively. The time of recovery from anesthesia and pulmonary infection after operation were recorded. The indices of immune function (NK cells, CD3+, CD4+ and CD8+ T lymphocytes) and stress response [C-reactive protein (CRP), norepinephrine (NE), epinephrine (E), adrenocorticotropic hormone (ACTH) and cortisol (COR)] were compared.

RESULTS: The time of recovery of spontaneous respiration, eye opening on calling and extubation of experimental group was shorter than that of control group (P<0.05). The experimental group had fewer cases of pulmonary infection, fever, cough, sputum production and pulmonary rales than control group (P<0.05). The number of NK cells, counts of CD3+ and CD4+ and CD4+/CD8+ ratio decreased markedly at T2 compared with those at T1 (P<0.05), and increased obviously at T3 in both groups (P<0.05). At T2 and T3, the above values were higher in experimental group than those in control group (P<0.05). Compared with T1, the levels of CRP, NE, E, ACTH and COR in both groups increased distinctly at T2 (P<0.05), but declined prominently at T3 (P<0.05). The experimental group had lower levels of these indices at T2 and T3 (P<0.05).

CONCLUSIONS: During the radical gastrectomy for elderly patients, general anesthesia combined with epidural anesthesia shortens the time of recovery from anesthesia, reduces the risk of postoperative pulmonary infection and significantly alleviates the suppression of immunity function and stress response, which is conducive to the prognosis.

KEYWORDS: Anesthesia, Radical Gastrectomy, Elderly, Infection, Immune Function, Stress Response

Introduction

The prognosis of patients with gastric cancer, one of the most common malignant tumors, has been improved due to advanced diagnostic techniques and better intraoperative and postoperative nursing levels, but the mortality rate of the gastric cancer patients still ranks second among all the cancer mortality rates in the world. Radical gastrectomy, a commonly used operative method for gastric cancer in present clinical practices, consumes a short time and results in exact efficacy. However, the operation itself is a strong stressor for the body, which is extremely prone to leading to metabolic imbalance, internal milieu disorder and various stress responses, thus causing great damage to the body [1]. As a

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frequently used anesthetic method, general anesthesia can easily cause restlessness during recovery, infection and reduction in immune function due to pain stimulation, electrolyte imbalance and other factors in the patients. General anesthesia combined with epidural anesthesia can block the afferent process of noxious stimuli to decrease harmful stimuli [2]. Selecting scientific and reasonable anesthesia protocols during radical gastrectomy is of great clinical significance. Currently, the effects of different anesthetic methods on the infection, immune function and stress response in elderly patients after radical gastrectomy have not been reported yet. In this research, therefore, 118 elderly patients treated with radical gastrectomy in our hospital from October 2016 to November 2019 were selected and given general anesthesia and general anesthesia combined with epidural anesthesia separately. The influences of the two anesthetic methods on the postoperative infection, immune function and stress response in the elderly patients were investigated, so as to provide guidance for the selection of scientific and reasonable anesthesia protocols for the elderly receiving radical gastrectomy.

Materials and Methods

BASELINE CLINICAL DATA

A total of 118 elderly patients undergoing radical gastrectomy in our hospital from October 2016 to November 2019 were selected as the subjects, and they were divided into control group (n=59) and experimental group (n=59) using a random number table. The patients in the control group received general anesthesia. There were 33 men and 26 women aged 65-83 years old, with an average of (71.58±6.24) years old, and their body weight was 42-76 kg, with an average weight of (60.32±2.87) kg. The general anesthesia combined with epidural anesthesia was applied in the observation group, which consisted of 31 men and 28 women aged 65-84 years old and (72.41±6.36) years old on average, and the body weight was 41-75 kg, with an average of (59.78±2.65) kg. The inclusion criteria were set by reference to related diagnostic criteria in the Chinese guidelines for diagnosis and treatment of gastric cancer 2018 [3] as follows: 1) the patients were diagnosed with gastric cancer by gastroscopy and tissue biopsy before operation. 2) The patients were aged >65 years old. 3) The patients were treated with radical gastrectomy. 4) The patients did not receive radiotherapy, chemotherapy, immunotherapy and molecularly targeted therapy before operation. 5) The patients had no massive hemorrhage and were administered with protein and blood products during and after operation. 6) The patients had an American Society of Anesthesiologists (ASA) grade for anesthesia risk < grade III. 7) The patients had complete clinical case data. 8) The patients voluntarily participated and positively cooperated in this research, and they signed the informed consent. Exclusion criteria: 1) the patients were complicated with endocrine system disease, immune system disease or cardiac, pulmonary, hepatic or renal insufficiency. 2) The patients had signs of infection or used hormone, non-steroidal drug or immunodepressant before operation. 3) The patients had a history of allergy to anesthesia. 4) The patients had severe trauma or coagulation abnormality. 5) The patients were complicated with language or cognitive disorders or mental diseases. This research was reviewed and approved by the Medical Ethics Committee of our hospital. The ASA grade for anesthesia risk [4] is classified into grade I (healthy people only have local lesion and no systemic disease), grade II (patients have mild and moderate systemic disease), grade III (patients have serious systemic disease and limited daily activities but no incapacity to work), grade IV (patients have incapacity to work as well as serious and life-threatening systemic disease) and grade V (patients are in a critical condition and need emergency rescue operation).

ANESTHESIA METHODS

All the patients were deprived of food and water at 8 h before operation, and their vital signs such as pulse, blood pressure and electrocardiogram were monitored. At 30 min before operation, 0.5 mg of atropine (NMPN H33020465, Zhejiang Ruixin Pharma Co., Ltd.) and 0.1 g of phenobarbital sodium (NMPN H12020381, Tianjin Kingyork Group Co., Ltd.) were injected intramuscularly to open the intravenous lines, and their volume was expanded by infusing Lactated Ringer's solution at the same time. The patients in the control group were given general anesthesia. Specifically, 0.2 mg/kg cisatracurium (NMPN H20060869, Jiangsu Hengrui Medicine Co., Ltd.), 4 μg/kg fentanyl (NMPN H42022132, Yichang Humanwell Pharmaceutical Co., Ltd.), 0.04 mg/kg midazolam (NMPN H10980026, Jiangsu Nhwa Pharmaceutical Co., Ltd.) and 1 mg/kg propofol (approval No.: H20130535, AstraZeneca UK Limited) were injected intravenously for anesthesia induction. 2-3 min later, tracheal intubation and mechanical ventilation were performed, and

cisatracurium (0.12 mg/kg/h), propofol (5-8 mg/kg/h) and fentanyl (0.05-0.25 μg/kg/h) were persistently infused via the vein to maintain the anesthesia during operation. Moreover, the patients in the experimental group were treated with general anesthesia combined with epidural anesthesia. In detail, the T8-T9 intervertebral space of the patients was selected as the puncture point, from which the puncture needle was inserted, and a feeling of emptiness indicated that the needle reached the epidural space. Next, an epidural catheter (3-4 cm) was implanted toward the head, through which 5 mL of 2% lidocaine (NMPN H31021072, Shanghai Zhaohui Pharmaceutical Co., Ltd.) was injected. Subsequently, the T4-T12 intervertebral space was preliminarily determined as the anesthesia plane, and the general anesthesia was performed after the epidural anesthesia met the operation requirements. Besides, the anesthesia induction and maintenance were conducted according to the methods adopted in the control group, and the patients were provided with tracheal intubation and mechanical ventilation. Clear breathing sounds in the lung suggested successful ventilation, and 4 mL of drugs were administered epidurally every 45 min. After successful anesthesia, the radical gastrectomy was implemented.

OBSERVATION INDICES

The fasting venous blood was collected from the patients before anesthesia (T1), at the end of operation (T2) and at 24 h after operation (T3), then coagulated and centrifuged. Afterwards, the serum was collected for later use.

The time of recovery from anesthesia after operation, including the recovery of spontaneous respiration, eye opening on calling and extubation, of the patients was recorded. Infection was determined in accordance with the Diagnostic criteria for nosocomial infection [5] issued by the Ministry of Health, including 1) positive bacterial culture of serum and body fluids, 2) white blood cell count $>10\times10^9$/L, 3) fever (body temperature >38°C), 4) signs of infection such as cough, sputum production and pulmonary rales, and 5) foci of infection displayed in X-ray or ultrasonography. The patients would be diagnosed with infection if they met 3 or more of the above items.

As for the indices of immune function, the natural killer (NK) cells and T lymphocyte subsets, such as cluster of differentiation 3 (CD3)+ mature T lymphocytes, CD4+ helper T lymphocytes and CD8+ suppressor T lymphocytes, were examined using a flow cytometer (BD FACSCalibur, USA), and the CD4+/CD8+ ratio was calculated.

In terms of the indices of stress response, C-reactive protein (CRP) was measured by means of scattering turbidimetry. Norepinephrine (NE) and epinephrine (E) were detected through enzyme-linked immunosorbent assay. Additionally, adrenocorticotropic hormone (ACTH) and cortisol (COR) in the serum were determined via radioimmunoassay.

STATISTICAL ANALYSIS

All data were statistically analyzed by SPSS 19.0 software. The quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Intragroup comparisons at different time points were performed by the paired t test, and intergroup comparisons at the same time point were conducted with the independent t test. The numerical data were represented as percentage (%) and subjected to the χ^2 test. $P<0.05$ was considered statistically significant.

Results

BASELINE CLINICAL DATA

There were no significant differences in gender, age, weight, ASA grade, tumor location, tumor stage, pathological classification, surgical method, surgical time, and intraoperative blood loss between the two groups (P>0.05) (Table I).

ANESTHESIA RECOVERY TIME

The time of recovery of spontaneous respiration, eye opening on calling and extubation in the experimental group was remarkably shorter than that in the control group (P<0.05) (Table II).

PULMONARY INFECTION

The experimental group had notably fewer cases of pulmonary infection, fever, cough, sputum production and pulmonary rales than the control group (P<0.05). There was no significant difference in the number of cases with WBC of $>10\times10^9$/L and inflammation disclosed by chest X-ray examination between the two groups (P>0.05) (Table III).

IMMUNE FUNCTION

The number of NK cells, the levels of CD3+ and CD4+ and the CD4+/CD8+ ratio were decreased markedly at T2 compared with those at T1 (P<0.05), and they were increased obviously at T3 in both groups (P<0.05). At T2 and T3, the number of NK cells was larger, and the levels of CD3+ and CD4+ as well as the CD4+/CD8+ ratio were higher in the experimental group than those in the control group, and the differences were

statistically significant (P<0.05). There was no significant difference in CD8+ cells at each time point and between the two groups (P>0.05) (Table IV).

STRESS RESPONSE

Compared with those at T1, the levels of CRP, NE, E, ACTH and COR in both groups were elevated distinctly at T2 (P<0.05), but they declined prominently at T3 (P<0.05). The experimental group exhibited lower levels of these indices than the control group at T2 and T3, with statistically significant differences (P<0.05) (Table V).

Discussion

The morbidity and mortality rates of gastric cancer, which is a digestive tract malignancy, rank high in China, and diet, environment, heredity and Helicobacter pylori infection are considered as vital precipitating factors for the disease [6]. Currently, radical gastrectomy is a commonly applied therapeutic method in clinic, and the increases in disease and age can lead to different degrees of immune dysfunction in the elderly patients. In addition, anesthesia and operation are highly prone to triggering systemic injuries such as stress response, inflammatory response and secondary oxidative injury in the body. Therefore, relieving stress response, improving the immune function and reducing infection are the key measures to guarantee the prognosis of the elderly patients after radical gastrectomy [7]. As an important manipulation in the perioperative period, anesthesia is capable of effectively alleviating the distress of patients. Different methods and depths of anesthesia have varying effects on the stress response and immune function of patients [8], so appropriate anesthetic methods are the vital precondition for stabilizing the postoperative stress response and immune function and decreasing infection in the elderly patients undergoing radical gastrectomy. Both general anesthesia and local anesthesia are clinical anesthesia methods, and the former mainly includes intravenous anesthesia and inhalation anesthesia, which can deprive the patients of spontaneous respiration. Hence, tracheal intubation must be utilized to enable sufficient gas exchange in the patients. However, such an invasive manipulation makes the respiratory tract directly exposed to the air and extremely vulnerable to infection [9]. Following general anesthesia, the hypercoagulable state and unstable hemodynamics in the body prolong the anesthesia time [10]. Besides, upon the operative stimulation on visceral organs, the diaphragmatic reflex is inhibited, low tidal volume occurs, the activity of the lower lung is reduced, and the effective coughing and sputum producing ability is weakened, thereby resulting in retention of secretions [11]. Epidural block is a frequently used anesthetic method. Specifically, local anesthetics are injected into the epidural space to block the spinal nerve roots, thus temporarily paralyzing the innervated areas. The epidural block is performed in most operations at and below the abdomen. The general anesthesia combined with epidural anesthesia or postoperative analgesia can not only decrease the dose of general anesthetics and prolong the anesthesia time simultaneously, but also produce a preferable analgesic effect after operation [12]. In this study, the time of recovery of spontaneous respiration, eye opening on calling and extubation in the experimental group was remarkably shorter than that in the control group (P<0.05), and there were notably fewer cases of pulmonary infection, fever, cough, sputum production and pulmonary rales in the experimental group than those in the control group (P<0.05). These results are consistent with the findings reported by Wang et al. [13] that the time of recovery from general anesthesia combined with epidural anesthesia is shortened clearly, and that the pulmonary infection rate is lowered prominently after operation.

Cellular immunity plays a pivotal role in the prevention of postoperative infection and rehabilitation in organisms, and its function is usually evaluated by specific immunocompetent cells such as NK cells and T lymphocytes in the body. NK cells can directly kill inflammatory factors and tumor cells [14]. CD3 molecule is expressed on the surface of mature T cells, and the decreased CD3+ level indicates an immunosuppressive state in the body [15]. However, CD4 and CD8 molecules are not expressed on the surface of mature T cells at the same time, and the antibodies against B cells produced by CD4+ can facilitate immune surveillance, while CD8+ is able to repress CD4+ and antibody production and attenuate the proliferative capacity of T cells. The immune function of organisms can be reflected by the CD4+/CD8+ ratio, and the decline in the ratio signifies the reduction or inhibition of the immune function in organisms [16]. According to the results in this research, the number of NK cells, the levels of CD3+ and CD4+ and the CD4+/CD8+ ratio were decreased markedly at T2 compared with those at T1 (P<0.05), and they were increased obviously at T3 in the two groups (P<0.05). Probably, the

disease progression at T1 induces immune dysfunction in the body, the immune function is further affected by anesthesia and operation at T2, and the immune dysfunction is gradually ameliorated as the body is recovered after operation at T3. Furthermore, no significant differences in the number of NK cells, the levels of CD3+ and CD4+ and the CD4+/CD8+ ratio were observed between the two groups at T1 ($P>0.05$), while these indexes were increased in the experimental group at T2 and T3 in comparison with those in the control group, displaying statistically significant differences ($P<0.05$). The above results imply that the general anesthesia combined with epidural anesthesia has fewer effects on the cellular immune function of the elderly patients, and it can distinctly relieve the suppression of immunity function.

It is well-documented that the incidence of stress response in organisms can trigger the changes in the levels of a variety of cytokines and proteins [17]. CRP, an early sensitive protein, often serves as an independent indicator for evaluating the severity of post-traumatic stress response. The hypothalamic-pituitary-adrenocortical axis can generate excitation, secret massive COR under the stimulation of pain and release angiotensin II, aldosterone, renin and other stress hormones as sensitive indices for the hypothalamic-pituitary-adrenocortical axis at the same time. Besides, the levels of ACTH and COR can be applied to assess the intensity of stress response [18]. In addition, the stress hormones NE and E are secreted when the activity of the sympathetic nervous system is enhanced [19]. The results of this research revealed that in comparison with those at T1, the levels of CRP, NE, E, ACTH and COR in both groups were elevated at T2, with statistically significant differences ($P<0.05$), but they declined prominently at T3 compared with those at T2 ($P<0.05$). These results illustrate that anesthesia and surgical trauma are crucial stressors which aggravate stress response in the body, and the stress response is weakened by the slow self-repair of the patients after operation. Compared with those at T1, the levels of CRP, NE, E, ACTH and COR in both groups were elevated distinctly at T2 ($P<0.05$), but they declined prominently at T3 ($P<0.05$), demonstrating that the elderly patients receiving general anesthesia combined with epidural anesthesia have milder stress response than those undergoing general anesthesia, which is in line with the reports of Liu et al. [20]. Possibly, the scope of epidural block is limited in the T4-T12 intervertebral space, so that the majority of sympathetic neurotransmission and primary pain afferent pathway are obstructed in the operative region, and the amount of afferent painful stimuli is reduced dramatically. Additionally, the general anesthesia can suppress the transmission of harmful stimuli into the central nervous system through the secondary afferent pathway, finally regulating the stability of endocrine.

Conclusions

In conclusion, during the radical gastrectomy for elderly patients, general anesthesia combined with epidural anesthesia prominently shortens the time of recovery from anesthesia, reduces the pulmonary infection rate after operation and significantly alleviates the suppression of immunity function and stress response, which facilitates the postoperative recovery of the elderly patients and has great clinical application value.

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Tables:

Table 1. **Baseline clinical data [case (%)] (x ± s)**

Item	Control group (n=59)	Experimental group (n=59)	X^2/t	*P*
Gender (case)			0.137	0.712
Male	33	31		
Female	26	28		
Age (year)	71.58±6.24	72.41±6.36	0.716	0.476
Body weight (kg)	60.32±2.87	59.78±2.65	1.062	0.291
ASA grade (case)			0.155	0.694
I	20	18		
II	39	41		
Tumor location (case)			0.197	0.657
Gastric fundus/ardia	12	14		
Gastric antrum	47	45		
Tumor stage (case)			0.044	0.834
II	15	16		
III	44	43		
Pathological classification (case)			0.136	0.712
Lowly differentiated adenocarcinoma	32	30		
Moderately differentiated adenocarcinoma	27	29		
Surgical method (case)			0.160	0.689
Radical proximal gastrectomy	17	19		
Radical distal gastrectomy	42	40		
Surgical time (min)	218.45±19.36	220.72±20.58	0.617	0.538
Intraoperative blood loss (mL)	167.63±12.59	171.24±13.16	1.523	0.131

Table 2. **Anesthesia recovery time.**

Item	Control group (n=59)	Experimental group (n=59)	t	*P*
Spontaneous respiration recovery (min)	12.83±4.75	5.48±2.06	10.904	0.000
Eye opening on calling	19.05±6.42	9.73±3.14	10.017	0.000
Extubation time (min)	18.76±5.91	12.57±4.35	6.479	0.000

Table 3. **Pulmonary infection and related indices [case (%)].**

Item	Control group (n=59)	Experimental group (n=59)	χ^2	*P*
Pulmonary infection (case)	13	4	5.567	0.018
Fever (>38°C)	15	4	7.591	0.006
Cough and sputum production	11	3	5.187	0.023
Pulmonary rales	14	2	10.412	0.001
WBC >10×10^9/L	10	5	1.909	0.167
Inflammation disclosed by chest X-ray examination	8	3	2.506	0.113

Table 4. **Immune function (x ± s).**

Item	Control group (n=59)	Experimental group (n=59)	t	*P*
NK (%)				
T1	19.85±2.36	20.04±2.37	0.436	0.663
T2	15.21±1.47[a]	16.95±1.63*[a]	6.089	0.000
T3	17.42±2.03[b]	19.14±2.18*[b]	4.435	0.000
$CD3^+$ (%)				
T1	58.92±5.74	58.16±5.83	0.714	0.477
T2	43.68±4.25[a]	47.29±4.64*[a]	4.407	0.000
T3	48.51±4.79[b]	52.78±5.15*[b]	4.663	0.000
$CD4^+$ (%)				
T1	36.19±3.54	35.92±3.48	0.418	0.677
T2	21.76±2.08[a]	26.31±2.57*[a]	10.571	0.000
T3	27.43±2.65[b]	30.28±3.04*[b]	5.428	0.000
$CD8^+$ (%)				
T1	22.69±2.21	22.24±2.35	1.071	0.286
T2	22.05±2.14	21.96±2.20	0.225	0.822
T3	21.97±2.16	22.51±2.17	1.355	0.178
$CD4^+/CD8^+$				
T1	1.59±0.53	1.61±0.56	0.199	0.842
T2	0.98±0.32[a]	1.21±0.39*[a]	3.502	0.001
T3	1.25±0.40[b]	1.45±0.47*[b]	2.489	0.014

Compared with control group, *P<0.05; compared with T1, [a]P<0.05; compared with T2, [b]P<0.05.

Table 5. ***Stress response (x ± s).***

Item	Control group (n=59)	Experimental group (n=59)	t	*P*
CRP (mg/L)				
T1	37.58±3.92	38.16±4.03	0.792	0.430
T2	59.43±6.11[a]	51.82±5.25*[a]	7.256	0.000
T3	48.72±4.85[b]	43.47±4.46*[b]	6.120	0.000
NE (mmol/L)				
T1	170.53±18.24	169.48±17.86	0.316	0.753
T2	286.79±29.65[a]	241.63±24.72*[a]	8.986	0.000
T3	235.48±22.97[b]	204.56±19.84*[b]	7.825	0.000
E (mmol/L)				
T1	14.85±1.53	15.02±1.56	0.598	0.551
T2	32.71±3.16[a]	27.63±2.79*[a]	9.257	0.000
T3	23.98±2.42[b]	18.47±1.95*[b]	11.097	0.000
ACTH (pg/mL)				
T1	29.14±3.06	28.69±2.97	0.811	0.419
T2	58.37±6.18[a]	49.53±5.02*[a]	8.528	0.000
T3	42.85±4.31[b]	37.74±3.86*[b]	6.784	0.000
COR (ng/mL)				
T1	131.58±14.27	130.92±14.06	0.253	0.801
T2	173.46±18.69[a]	154.83±16.17*[a]	5.790	0.000
T3	148.72±15.21[b]	136.29±14.38*[b]	4.561	0.000

Compared with control group, *P<0.05; compared with T1, [a]P<0.05; compared with T2, [b]P<0.05.