European Review for Medical and Pharmacological Sciences 2018; 22: 2854-2859

Remifentanil on T lymphocytes, cognitive function and inflammatory cytokines of patients undergoing radical surgery for cervical cancer

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Abstract. – OBJECTIVE: To explore the effects of remifentanil on cognitive function, T lymphocyte subsets and inflammatory cytokines of patients undergoing radical surgery for cervical cancer.

PATIENTS AND METHODS: A total of 70 patients undergoing radical surgery for cervical cancer in our hospital from August 2014 to January 2017 were selected. They were divided into control group (n=35) and experimental group (n=35). The patients in the control group received intravenous drip of fentanyl, while those in the experimental group received intravenous drip of remifentanil in the surgery. All the patients returned to the wards after surgery. The eye-opening time, extubation time and awaking time of the patients were collected and recorded by specialized surgical nurses. Moreover, the cognitive function of the patients was assessed at the beginning of the surgery and 3 h, 6 h, 12 h, and 24 h after surgery. Blood was drawn at 24 h after surgery, and quantitative analysis of T lymphocyte subsets and inflammatory cytokines of the patients was conducted.

RESULTS: The eye-opening time, extubation time, and awaking time in the remifentanil group were significantly earlier than those in the fentanyl group after surgery ($p<0.05$). At the same time after surgery, the score of mini-mental state examination (MMSE) in the remifentanil group was higher than that in the fentanyl group. The difference was statistically significant ($p<0.05$). The patients in the experimental group had a relatively low occurrence of cognitive disorder after surgery ($p<0.05$). The impacts of remifentanil on each type of T lymphocytes and inflammatory cytokines of the patients after surgery were smaller than those of fentanyl. The differences were statistically significant ($p<0.05$).

CONCLUSIONS: Remifentanil can wake patients up early after surgery. Meanwhile, it results in small inflammatory response and stress response, and low occurrence of postoperative cognitive dysfunction in patients. Therefore, it is worthy of being vigorously promoted for clinical application.

Key Words:
Remifentanil, Fentanyl, Cervical cancer, Cognitive dysfunction, Inflammatory cytokines.

Introduction

Cervical cancer, also known as the number one killer of women, frequently occurs in middle-aged and elderly women. It is characterized by high morbidity and high mortality in females. Radical surgery for cervical cancer supplemented by postoperative radiotherapy is generally used in clinical practice[1]. Simple epidural anesthesia is usually adopted in radical surgery for cervical cancer in the past, but such way of anesthesia will make the patients experience an abdominal viscera traction reaction in the surgery, which leads to different degrees of stress response in the patients, thus making the patients feel uncomfortable in the surgery[2]. The occurrence of the stress response is mainly related to the secretion of endocrine hormones such as corticotropin, glucagon, and glucocorticoid because of the irritation to the body, which will induce the patients to suffer from hyperglycemia, sympathetic nerve excitement, etc.[3], resulting in neurological disorder in patients. The symptom is manifested as insanity, amnesia, inattention, restlessness, etc., which is also known as postoperative cognitive dysfunction[4]. Also, the patient can also suffer from immune dysfunction, decreased T lymphocytes and granulocytes, as well as different degrees of other complications after surgery[5,6]. As a μ-opioid

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receptor agonist, remifentanil can rapidly reach the blood-brain equilibrium in the body with rapid onset of action[7]. Meanwhile, the special ester bond structure in remifentanil enables it to be rapidly degraded to inactive remifentanil acid in the body and is excreted *via* the liver and the kidney without causing a large amount of accumulation in the body that can result in a dose-dependent poisoning reaction[4,7]. Remifentanil is characterized by rapid onset of anesthesia, few adverse reactions, etc. in orthopedic surgery. It is a new short-acting intravenous general anesthetic[5]. However, other studies have also reported that remifentanil may exert an impact on the postoperative cognitive function of the patients.

The effects of remifentanil on the cognitive function, inflammatory cytokines and T lymphocytes of the patients undergoing radical surgery for cervical cancer were discussed in this study to actively find a safe and effective method of anesthesia for patients undergoing radical surgery for cervical cancer.

Patients and Methods

Patients

A total of 70 patients undergoing radical surgery for cervical cancer in our hospital from August 2014 to January 2017 were selected. All of them reached Grade I or Grade II based on American Standards Association (ASA) grading. This study was approved by the Ethics Committee of Red Flag Hospital Affiliated to Mudanjiang Medical College. Signed written informed consents were obtained from all participants before the study. They were divided into control group (n=35) and experimental group (n=35). The weight, age, T-lymphocyte count, inflammatory cytokines, mini-mental state examination (MMSE) scores, duration of the surgery, ASA grade, etc. of the two groups of patients were comparable ($p>0.05$) (Table I).

Methods

Intravenous access was established for the 70 patients after they entered the surgery room. All of them received a conventional treatment (intramuscular injection of diazepam and atropine). Meanwhile, the patients in the observation group were given 0.3 μg/(kg·min) fentanyl by intravenous pumping at a maintenance dose of 1 μg/kg in the surgery. Those in the experimental group were given 0.3 μg/(kg·min) remifentanil by intravenous pumping at a maintenance dose of 3 μg/kg in the surgery. The two groups of patients were linked to a respirator and intubated for ventilation. The tidal volume was kept within 9 mL/kg^{-10} mL/kg for the patients in the surgery, and the respiratory rate was maintained at 10 breaths/min. The tube was drawn after the patient's spontaneous breathing was recovered, and the tidal volume reached the normal level.

Observation Indicators

The postoperative awaking time, eye-opening time and extubation time of the patients were observed and recorded. Moreover, the scores of cognitive function of the patients before surgery and at 3 h, 6 h, 12 h and 24 h after surgery were assessed based on MMSE scale[6]. Among them, the score <26 points was regarded as cognitive dysfunction. Peripheral venous blood was taken from the patients before induction of anaesthesia, after the beginning of the surgery and on the 1st day after surgery. Red blood cell lysate was added to degrade red blood cells, and the supernatant was removed by centrifugation. Then the percentages of T lymphocyte subtypes [cluster of differentiation 3 (CD3)$^+$, CD4$^+$ and CD8$^+$) were detected *via* flow cytometry. Blood was taken from the patients before induction of anaesthesia and in the surgery to detect the contents of each inflammatory cytokine in the serum using immunity transmission turbidimetry.

Statistical Analysis

Prim 5.0 software was used for statistical analysis of the data. The measurement data and the enumeration data were analyzed using the *t*-test and chi-square test, respectively. $p<0.05$ suggested a statistical difference.

Results

Comparisons of Basic Data Between the Two Groups of Patients

There were no differences in basic data (including the weight, age, and ASA grade) between the two groups of patients. The data were comparable ($p>0.05$) (Table I).

Comparison of Detection Results of T Lymphocytes Between the Two Groups of Patients

Compared with those before induction of anesthesia, T lymphocytes (CD3$^+$ and CD4$^+$) in the two groups of patients were decreased ($p<0.05$),

$CD8^+$ in the control group was reduced ($p<0.05$), while they had no significant changes in the experimental group ($p>0.05$) in the surgery and at 24 h after surgery. Compared with those in the control group, $CD3^+$ of the patients in the experimental group was decreased significantly, while $CD4^+$ and $CD8^+$ were increased ($p<0.05$), which showed statistical differences (Table II).

Comparisons of Cognitive Function and MMSE Scores Between the Two Groups of Patients

The awaking time, extubation time and eye-opening time of the patients in the remifentanil group were earlier than those of the patients in the control group ($p<0.05$). The MMSE scores in the remifentanil group and the fentanyl group at 3 h after surgery were notably lower than those before surgery ($p<0.05$). At 6 h, 12 h and 24 h after surgery, the MMSE scores of the two groups of patients were increased in turn, and all the scores in the remifentanil group were higher than those in the fentanyl group ($p<0.05$). (Table III).

Comparison of the Occurrence of Cognitive Dysfunction Between the Two Groups of Patients

The occurrence of cognitive dysfunction in the remifentanil group was 51.4% (18 patients) at 3 h after surgery, 25.7% (9 patients) at 6 h after surgery and 3% (1 patient) at 12 h after surgery. The results were markedly low-

Table I. Comparisons of basic data between the experimental group and the control group ($\bar{x} \pm s$).

Group	Weight (kg)	Age (Y)	ASA grade			
			Ia	Ib1	Ib2	IIa
Control group (n=35)	55.8±6.92	56.4±3.17	6	21	4	4
Experimental group (n=35)	55.9±2.79	57.2±3.28	7	20	5	3

Table II. Comparison of detection results of T lymphocytes between the two groups of patients ($\bar{x} \pm s$).

Group	T lymphocyte typing	Before induction of anesthesia	In the surgery	At 24 h after surgery
Control group (n=35)	CD3+	71.21±14.32	67.57±3.86	60.98±2.74
	CD4+	45.64±8.26	39.83±8.72	35.69±7.58
	CD8+	26.17±8.29	22.45±7.48	21.32±4.09
	CD4+/CD8+	1.67±0.84	1.72±0.74	1.72±0.64
Experimental group (n=35)	CD3+	69.53±16.15	62.49±2.83*	57.59±3.15*
	CD4+	43.53±7.63	41.89±9.26	42.59±8.69
	CD8+	27.63±7.26	27.18±6.63#	26.97±7.59#
	CD4+/CD8+	1.73±0.74	1.69±0.78	1.72±0.57

Table III. Comparisons of cognitive function and MMSE scores between the experimental group and the control group ($\bar{x} \pm s$).

	Control group	Experimental group
Eye-opening time (min)	16.5±2.5	8.5±3.5**
Extubation time (min)	23.5±3.5	15±2.5*
Response time (min)	24.6±4.5	17.5±1.5*
Before surgery	28.4±2.2	27.9±3.1
At 3 h after surgery	18.5±2.6	20.3±2.7
At 6 h after surgery	20.7±3.4	24.6±2.7*
At 12 h after surgery	22.6±2.6	25.3±2.5*
At 24 h after surgery	24.8±2.5	27.3±3.5**

Note: Compared with the control group, *$p<0.05$.

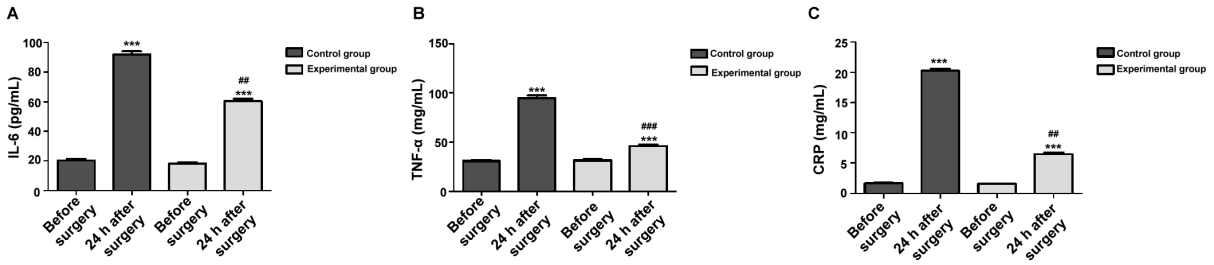

Figure 1. ***A,*** Comparison of the level of IL-6 between the two groups of patients. ***B,*** Comparison of the level of TNF-α between the two groups of patients. ***C,*** Comparison of the level of CRP between the two groups of patients.

er than those [74.3% (26 patients), 51.4% (18 patients) and 20% (7 patients)] in the control group. The differences were statistically significant ($p<0.05$). Moreover, the MMSE scores of the two groups of patients basically returned to the normal level at 24 h after surgery ($p=0.31$, $p>0.05$) (Table IV).

Comparisons of the Levels of Inflammatory Cytokines after Surgery Between the Two Groups of Patients

There were no remarkable differences between the two groups of patients in terms of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) before surgery. They were comparable ($p>0.05$). Also, the levels of the aforementioned indicators in the two groups at 24 h after surgery were higher than those before surgery, but the levels in the experimental group were lower than those in the control group ($p<0.05$) (Figure 1).

Discussion

The radical surgery for cervical cancer has a relatively high requirement for anesthesia in the surgery due to the general low T lymphocytes in patients and the difficulty of grasping the overall operation time. Moreover, it is easy for traditional anesthesia with tracheal intubation to induce a stress response in the patients. Therefore, it is urgent to develop a new anaesthetic with rapid onset of action, fast degradation, small toxic or side effects and no dose accumulation in the patients. As a kind of fentanyl, remifentanil has the advantages such as rapid onset of action, fast metabolism, few adverse reactions and dose-independence[4,8]. It has been widely used as a short-acting intravenous general anesthetic in large surgeries such as orthopedic surgery due to its advantages such as quick onset of anesthesia and few adverse reactions[5,9]. Choi et al[10] showed that remifentanil in combination with propofol can inhibit the proliferation of lymphocytes and the release of inflammatory factors into the blood, and reduce the inhibitory effect on the nervous system, thereby reducing postoperative inflammatory response and stress response and shortening the postoperative awaking time for the patients. Wei et al[11] proved that, in the orthopedic surgery, intravenous anesthesia with remifentanil and propofol not only has the advantages of rapid onset of action and few adverse reactions, but also exerts small impacts on blood pressure and heart rate of the patients, which is

Table IV. Comparison of the occurrence of cognitive dysfunction between the experimental group and the control group (n, %).

Group	At 3 h after surgery	At 6 h after surgery	At 12 h after surgery	At 24 h after surgery
Control group (n=35)	26 (74.3)	18 (51.4)	7 (20)	1 (3)
Experimental group (n=35)	18 (51.4)	9 (54.3)	1 (3)	0 (0)
Chi-square value	2.8	3.1	3.2	1.1
p-value	0.047*	0.027*	0.024*	0.31
At 24 h after surgery	24.8±2.5	27.3±3.5**		

Note: Compared with the control group, *$p<0.05$.

particularly suitable for frail patients with high sensitivity to drugs and poor body resistance, especially for elderly patients. Various factors such as decreased body function and degenerative diseases in the respiratory, cardiovascular and immune systems are prone to induce postoperative cognitive dysfunction in the patients[12,13]. Therefore, it is the striving aim of clinical anesthesia to find out and develop a safe and effective anesthetic with low toxicity so as to shorten the postoperative extubation time and awaking time and reduce each kind of postoperative residual effects for the patients, thereby helping patients recover faster after surgery[14-16]. Watanabe et al[14] further confirmed that as an anaesthetic, remifentanil causes a relatively small injury to the nervous system, and the patients' cognitive function can return to normal within a short time after surgery[17,18]. Given the above study results, the clinical data and each indicator of the patients were collected in this study to further observe the influence of the anaesthetic (remifentanil) on the patients, thus providing a scientific basis for clinical exploration of new anaesthetics. The results of this study showed that remifentanil could shorten the postoperative awaking time, eye-opening time and extubation time and lower the impacts of the drug on cognitive function of the patients. Meanwhile, remifentanil could also inhibit the proliferation of T lymphocytes and the release of inflammatory cytokines, thus relieving postoperative inflammatory response and stress response in the patients.

Conclusions

Remifentanil has relatively small impacts on the cognitive function, T lymphocytes and inflammatory cytokines of the patients undergoing radical surgery for cervical cancer. It was safe and worthy of further validation and promotion for clinically surgical anesthesia.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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