

Effects of Remifentanyl Combined with Gastrodin Injection on Cerebral Oxygen Metabolism and Early Postoperative Cognitive Function in Patients Undergoing Laparoscopic Surgery for Cervical Cancer

Xu Changgui

Suzhou Dongwu Hospital Intergrating Traditional Chinese & Western Medicine

ABSTRACT

ARTICLE INFO

Article history:

Published online: 31st Jan, 2018

Key words:

Remifentanyl

Gastrodin injection

Cerebral metabolism

Cognitive function

Objective Effects of Remifentanyl combined with Gastrodin injection on cerebral oxygen metabolism and early postoperative cognitive function in patients undergoing laparoscopic surgery for cervical cancer. **Methods** 107 cases of laparoscopic cervical carcinoma were randomly divided into observation group (54 cases) and control group (53 cases), the control group received anesthesia induction therapy based on Remifentanyl, the observation group was given intravenous Gastrodin injection to 120h after operation on the basis of control group. the brain oxygen metabolism and brain injury related indexes 6h, 12h, 72h and 120h after operation were observed, and the preoperative cognitive function and postoperative cognitive function of two groups after 6h, 1d, 3d and 5d were evaluated by using Mini-Mental State Examination (MMSE) test method. **Results** Compared to the preoperative data, the oxygen saturation of the internal jugular vein (SjvO₂) and cerebral oxygen saturation (rSO₂) of two groups after 6h of operation was significantly decreased (p <0.05), and the indexes all back to normal after 120h, and observation group's indexes were higher than that in control group (P <0.05); and the Cerebral arterial - venous oxygen content difference (Da-jvO₂) and Cerebral Oxygen extraction rate (CERO₂) of two groups after 6h of operation was significantly increased (P <0.05), and the indexes all back to normal after 120h and observation group's indexes were lower than that in control group (P <0.05); serum neuron specific enolase(NSE) and S100B protein level of two groups after

6h of operation was significantly increased and back to normal after 120h, and observation group's indexes were lower than that in control group ($P < 0.05$); The MMSE score of 6h, 12h, 72h and 120h were higher in the observation group than in the control group, and the incidence of postoperative cognitive dysfunction (POCD) was lower than that in the control group ($P < 0.05$).

0 Introduction

The related research shows that postoperative cognitive dysfunction (POCD) is a common central nervous system complication after gynecologic laparoscopic surgery [1], which is closely related to operation, anesthesia and anesthesia depth, mainly manifested in early postoperative personality changes, memory impairment, mental disorders and anxiety and other symptoms, having adverse effects on postoperative rehabilitation[2]. Intravenous inhalation combined anesthesia is a commonly used ideal anesthetic program in clinic, and at present, it has been widely used in gynecological laparoscopic surgery. Remifentanyl is an important short-acting opioid drugs in intravenous anesthesia, and the drug has advantages like fast metabolism, quick wakeness after recovery, but relevant research confirms that opioid drugs can adversely affect the cognitive function of patients [3]. In recent years, with the continuous progress of anesthesia technology, POCD has aroused the attention of clinical anesthesia physicians, but how to reduce the incidence of POCD and promote recovery of patients has become an urgent problem for the anesthesiologist. This research has observed the effects of Remifentanyl combined with Gastrodin injection on cerebral oxygen metabolism and early postoperative cognitive function

Conclusion In the anesthesia induction program based on Remifentanyl, the use of Gastrodin injection can reduce the incidence of cognitive dysfunction after laparoscopic surgery for cervical cancer, and its mechanism may be related to the improvement of brain metabolism and the reduction of hypoxia injury in neurons of cranial nerves.

in patients undergoing laparoscopic surgery for cervical cancer, and the report is as follows.

1 Clinical Materials

1.1 General materials

From February 2015 to July 2016, 107 patients undergoing laparoscopic surgery for cervical cancer in our hospital were selected as cases for the study, age 25~60 years old, Asa II ~ III grade, International gynecology and obstetrics union cervical cancer Clinical staging standard (FIGO) [4]: IA~IIA period; both patients and their families signed informed consent. Patients who have had opioid or diazepam drugs for a long term, who had alcoholism and drug abuse history, psychiatric history, neurological diseases, diabetes mellitus, hypertension, preoperative severe liver and kidney insufficiency, infection, malignant tumor in other parts, immunodeficiency disease, coagulation dysfunction, blood system disease were all excluded in the study. 107 patients were randomly divided into observation group (54 cases) and control group (53 cases). There was no statistically significant difference in age, body mass index (BMI), FIGO stage, pathological type, operation time, anesthesia time and education level between the two groups ($P > 0.05$), so they are comparable. See table 1.

Groups	Ca ses	Age (year s old)	BMI(K g/m ²)	Pathological type (n)			Clinical staging of cervical cancer (n)			Opera tion time(h)	anesth esia time (h)	education level		
				S C C	adenocarc inoma	adenosqu amous carcinom a	I A	I B	II A			Jun ior Hig h and Bel ow	Senio r High Schools and Middl e Speci ality Schoo ls	Coll ege or abov e
Observ ation group	54	43.2 ±5.5	43.2±5. 5	9	41	4	1 7	2 0	1 7	4.1±1 .0	4.8±1. 1	15	26	13
Control group	53	45.6 ±6.2	45.6±6. 2	10	40	3	1 5	2 2	1 6	4.2±1 .2	5.0±1. 5	17	25	11
<i>t/χ²</i>		0.32 9	0.226	0.189			0.415		0.275	0.893	0.164			
<i>P</i>		>0.0 5	>0.05	>0.05			>0.05		>0.05	>0.05	>0.05			

Table 1. Comparison of general clinical data of two groups before treatment

1.2 Treatment

2 Groups were fasted for 8h before operation, and were injected morphine hydrochloride injection(0.2mg/kg) by intramuscular injection 30 minutes before anesthesia, and their heart rate, blood pressure, blood oxygen saturation and other data were measured by PM-8000 ECG monitor produced by Mai Rui

Company after they entering the operating room. (1) The control group received anesthesia induction therapy based on remifentanyl, and patients were injected remifentanyl (2μg/kg), propofol (1.5mg/kg) and vecuronium bromide (0.1mg/kg) by intravenous injection, then were given endotracheal intubation for mechanical ventilation (pattern: IPPV), Respiration parameters: Respiration frequency is 12~16times/ min,

respiration ratio is 1:2, tidal volume 8~10 ml/kg, and laparoscopic CO₂ pneumoperitoneum is around PECO₂ 35~45 mmHg. During the anesthesia maintenance phase, continuous intravenous infusion of 1~2μg/(kg·h) remifentanyl, 4~12mg/(kg·h) propofol, 0.1~0.3mg/(kg·h) vecuronium bromide was given by microelectric pump infusion. (2) The observation group, on the basis of the control group, was given gastrodin injection (Kunming Pharmaceutical Co., Ltd.), the use is: 600mg+250 ml 0.9% normal saline intravenous drip, 1d before operation, 1 time/d, until 120h (5d) after surgery.

1.3 Parameters

(1) brain metabolism-related indexes: internal jugular vein bulb oxygen saturation (SjvO₂), cerebral oxygen saturation (rSO₂), cerebral arterial-venous blood oxygen content difference (DA-JVO₂) and brain oxygen uptake (CERO₂) of the two groups were observed 6h, 12h, 72h and 120h after the operation; (2) The indexes related to brain injury: serum neuron-specific enolase (NSE) and S100B protein levels of the two groups were observed 6h, 12h, 72h and 120h after operation; (3) The cognitive functions patients in two groups 6h, 12h, 72h, 120h after operation were evaluated by using Mini-Mental State Examination (MMSE) [5] test methods. The total score

of MMSE was 30 points, the mild cognitive dysfunction (POCD) was 24~27 points, the median was 19~23, the severe was 0~18, and the POCD incidence of the above time was recorded.

1.4 Statistical method

Using SPSS19.0 statistical software to analyze, and the normal distribution of the measurement data was indicated by $(\bar{x} \pm s)$, t test was used in processing, counting data was indicated by rate or composition ratio, data processing indicated by χ^2 test, $p < 0.05$ means that the difference is statistically significant.

2 Results

2.1 Comparison of related indexes of brain metabolism between two groups before and after operation

The SjvO₂ and rSO₂ of 6h after operation in two groups was significantly lower than preoperative ($P < 0.05$), and 120h after the operation was gradually back to normal; the above indexes of observation group were higher than that in the control group ($P < 0.05$), and the Da-jvo₂ and CERO₂ of 6h after operation in both groups were significantly higher than that before operation ($P < 0.05$). See table 2.

Group	SjvO2(%)					Da -jvO2(ml/L)				
	Before operation	6h after operation	12h after operation	72h after operation	120h after operation	Before operation	6h after operation	12h after operation	72h after operation	120h after operation
Observation group	60.2±5.3	55.1±3.8 ^①	57.2±4.0 ^①	59.2±5.5	62.5±3.4	42.5±3.5	48.0±3.4 ^①	45.3±3.7 ^①	42.0±3.5	41.1±3.4
Control group	60.5±5.8	52.2±4.2 ^①	54.7±4.1 ^①	56.5±4.8 ^①	58.1±4.0	43.1±3.8	51.8±3.7 ^①	48.8±3.5 ^①	46.1±3.0 ^①	44.3±4.2
<i>t</i>	0.218	3.278	3.174	3.773	3.254	0.287	4.219	5.783	4.773	4.083
<i>P</i>	>0.05	<0.05	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05

Groups	CERO2(%)					rSo2(%)				
	Before operation	6h after operation	12h after operation	72h after operation	120h after operation	Before operation	6h after operation	12h after operation	72h after operation	120h after operation
Observation group	36.1±3.5	43.2±4.0 ^①	40.1±4.1 ^①	37.0±3.5	35.1±3.1	71.2±4.5	64.3±4.5 ^①	67.3±5.2 ^①	70.2±4.8	72.1±4.5
Control group	37.2±3.0	47.4±4.1 ^①	44.5±3.9 ^①	41.8±3.6 ^①	38.4±3.4	70.7±5.2	61.1±4.8 ^①	64.0±3.9 ^①	66.4±4.5 ^①	69.0±4.4
<i>t</i>	0.208	3.874	4.004	3.908	4.235	0.174	3.562	4.410	4.058	4.276
<i>P</i>	>0.05	<0.05	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05

Table 2. Comparison of related indexes of brain metabolism between two groups before and after operation

$\bar{x} \pm s$

Note: ① was compared by data before treatment, $P < 0.05$

2.2 Comparison of serum S100B and NSE levels between the two groups at different time points before and after operation

The two indexes 120h after operation gradually recovered to normal, and the indexes of the observation group were lower than those in the control group ($P < 0.05$), and the serum NSE and S100B

protein level in the two groups was significantly lower than that of preoperative ($P < 0.05$), 120h after operation they gradually recovered to normal, and the

observation group was lower than the control group ($P < 0.05$). See table 3.

Group	S100B(pg/mL)					NSE(pg/mL)				
	Before operation	6h after operation	12h after operation	72h after operation	120h after operation	Before operation	6h after operation	12h after operation	72h after operation	120h after operation
Observation group	0.95±0.1 5	1.12±0.21 ^①	1.05±0.19 ^①	0.99±0.13	0.96±0.1 1	8.21±1.1 6	10.13±1.2 5 ^①	9.36±1.1 7 ^①	8.53±1.1 4	8.15±1.1 21
Control group	0.97±0.1 6	1.23±0.25 ^①	1.16±0.20 ^①	1.07±0.16 ^①	0.99±0.1 4	8.24±1.1 5	12.34±1.3 0 ^①	10.87±1.1 24 ^①	9.73±1.1 8 ^①	8.45±1.1 08
<i>t</i>	0.260	5.378	6.274	5.887	4.843	0.338	5.218	5.675	5.164	4.987
<i>P</i>	>0.05	<0.05	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05

Table 3. Comparison of serum S100B and NSE levels between the two groups at different time points before and after operation ($\bar{x} \pm s$)

Note: ① was compared by data before treatment, $P < 0.05$.

2.3 Comparison of MMSE score and POCD incidence rate between the two groups before and after operation at different time points

The MMSE score of 6h, 12h, 72h and 120h after operation were observed and those were higher in the observation group than in the control group, and the postoperative POCD incidence rate was lower than that of the control group. ($P < 0.05$)

Group	MMSE score					POCD incidence rate				
	Before operation	6h after operation	12h after operation	72h after operation	120h after operation	Before operation	6h after operation	12h after operation	72h after operation	120h after operation
Observation group	27.20±2.47	25.10±2.54 ^①	25.67±2.88 ^①	26.71±1.65	27.15±1.40	0(0.0)	3(5.5)	2(3.7)	1(1.9)	0(0.0)
Control group	27.45±2.26	22.24±2.29 ^①	23.56±2.74 ^①	25.08±1.54 ^①	25.72±1.34	0(0.0)	8(15.1)	7(13.2)	5(9.4)	3(5.7)
<i>t</i>	0.478	4.983	3.114	3.732	3.187	0.309	4.983	5.254	4.865	4.547
<i>P</i>	>0.05	<0.05	<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05

Table 4. Comparison of MMSE score and POCD incidence rate between the two groups before and after operation at different time points

Note: ①was compared by data before treatment, $P < 0.05$.

3 Discussion

Cervical cancer is the most common malignant tumor in gynecology, which can seriously affect the life and health of female patients. Laparoscopic surgery has now become the preferred treatment for cervical cancer^[6], although the operation has the advantages of small trauma, rapid recovery of patients after operation and other advantages, but because of the use of static inhalation combined anesthesia, and anesthesia drugs can inhibit the central cholinergic nervous system and inhibit the synthesis and release of acetylcholine, so there may be a certain degree of cognitive dysfunction in patients after operation. Related studies show that^[7], the incidence of POCD after gynecological laparoscopic surgery is 12.4%~28.4%, which occurs within 1 week, especially 6h~12h after the operation the incidence rate was the highest. Related research shows^[8] that the abnormal brain metabolism in laparoscopic surgery plays an important role in the

pathogenesis of POCD, and because the CO₂ pneumoperitoneum in laparoscopic surgery causes the diaphragm to lift the patient's chest pressure, which leads to the increase of venous reflux resistance in the brain and CO₂ accumulation in cerebral blood vessel dilation, eventually causing hyperemia and brain damage. On the other hand, anesthetic drugs such as remifentanyl and propofol can cause cerebral oxygen metabolic rate decreased, brain tissue perfusion insufficiency and brain cell oxygenation function decreased, and can also induced the occurrence of POCD. The related study also confirmed that postoperative patients with gynecological laparoscopic surgery showed significantly decreased SjvO₂, rSO₂ brain metabolic index 6h~12h after operation, and DA-JVO₂ and CERO₂ were significantly increased, and is positively correlated with the occurrence time of POCD^[9]. In addition, brain metabolic abnormalities can cause a certain degree of nerve cell damage, and

the serum NSE and S100B protein level are two important indexes to reflect the function of brain cell injury and nerve defect. When the brain cell membrane is stimulated by inflammation and hypoxia, the NSE and S100B proteins overflow from the damaged brain cells to the peripheral blood, and then its content was significantly increased. Related studies showed that^[10] the serum NSE and S100B protein level in patients with impaired cognitive function was negatively correlated with the S_{jo}O₂ and rSO₂ of brain metabolic indices and negatively correlated with the MMSE score of cognitive function.

Remifentanyl is a kind of opioid drugs with the shortest time of function, and it metabolizes mainly through the rapid elimination of drug metabolism, so its analgesic effect of anesthesia is better than fentanyl and is suitable for static inhalation of combined anesthesia for middle-aged and elderly patients with cervical cancer^[11]. In addition, the drug does not affect the liver and kidney function, has small affection on respiratory system of patients, is very safe, and can also reduce inhibition to respiratory system and cognition from other anesthetic drugs on the patients. However, related research shows that remifentanyl still has a certain adverse effect on the cognitive function of patients, and the mechanism of which may be caused by hemodynamic, oxidative stress, abnormal brain metabolism and other ways, causing POCD^[12]. In this study, Gastrodin injection is the extract of *Gastrodia elata*, and its active ingredient of the drug is 4-hydroxy-phenyl -beta-D thiogalactoside-pyrrole, and the previous study showed that the drug achieved good results in treatment of cerebral infarction, high blood pressure vertigo, vertebral-basilar artery insufficiency and other diseases. Modern pharmacology studies show^[13] that Gastrodin injection can inhibit the reduction of peripheral vascular resistance, improve microcirculation, improve the compliance of blood vessel dilation, increase the blood supply of nerve cells to provide oxygen, and maintain the integrity of the

brain cell membrane. Animal experiment confirmed^[14] that Gastrodin can affect the nerve remodeling in rats hippocampal when brain injury, and through the influence of brain-derived nutrition factor (BDNF) and mRNA expression of synaptic (Syn I), so as to improve the cognitive function of brain injury rats. Gastrodin injection can also significantly improve the tension of cerebrovascular, regulate hemodynamics, promote blood supply of brain tissue, and increase the oxygenation function of brain cells^[15]. In addition, Gastrodin injection can inhibit oxidative stress reaction, remove excess oxygen free radicals in brain tissue, reduce lipid peroxidation damage in brain cells, and improve cognitive function of patients^[16].

The results of this study showed that the S_{jo}O₂ and rSO₂ was significantly lower 6h after operation than before operation, and after 120h, they were gradually restored to normal, and the indexes of observation group were higher than those in control group; and the Da-jvo₂ and CERO₂ of 6h after operation were significantly higher than before, after 120h, they were gradually restored to normal, and the indexes of the observation group were lower than those in the control group; and the serum NSE and s100b protein level in the two groups were significantly lower than that of preoperative patients, after 120h, they were gradually restored to normal, and these indexes of the observation group were lower than those of the control group; the MMSE score of 6h, 12h, 72h and 120h after operation were higher in the observation group than in the control group, and the incidence of postoperative cognitive dysfunction (POCD) was lower than that in the control group, which suggested that in the anesthesia induction program based on Remifentanyl, the use of Gastrodin injection can reduce the incidence of cognitive dysfunction after laparoscopic surgery for cervical cancer, and its mechanism may be related to the improvement of brain metabolism and the reduction of hypoxic injury in neurons.

References

- [1] Cui Jing, Li Shaoyan. Effect of Different Doses of Dexmedetomidine on Postoperative Cognitive Function in Gynecologic Laparoscopic Surgery Patients[J]. *Maternal and Child Health Care of China*,2014,29 (8) :1286-1288
- [2] Sun Zhentao, Sun Xueqing, Han Xueping, etc. Effects of Different Respiration Parameters on Early Cognitive Function after Gynecologic Laparoscopic Surgery [J]. *Journal of Clinical Anesthesiology*,2014,30(7):686-688
- [3] Li Xue, Zhu Ming. Effect of Propofol and Reventani Combined Anesthesia on Postoperative Cognitive Function in Elderly Patients Undergoing Laparoscopic Cholecystectomy[J]. *Medical Recapitulate*,2016,22(10):1970-1973
- [4] Li Xue, Kong Weimin, etc. Change Trends of Incident Rate in Cervical Cancer of Beijing Obstetrics and Gynecology Hospital, Capital Medical University from 1992 to 2011 [J]. *Chinese Journal of Obstetrics & Gynecology and Pediatrics (Electronic Edition)*,2013,9(3):310-314.
- [5] Tang Hang, Zhang Peijun, Zheng Kunwen, etc. Effect of Shenfu Injection on Postoperative Cognitive Function in Elderly Patients Undergoing Abdominal Surgery [J]. *Guangdong Medical Journal*,2013,34(18):2861-2863
- [6] Zhang Lili, Hao Min, Zhao Weihong. Clinical Value of Laparoscopic Radical Resection of Pelvic Nerves for Cervical Cancer [J]. *Chinese Journal of Laparoscopic Surgery (Electronic Edition)*,2014,7(2):116-120
- [7] Cui Min, Si Jiguo, Gai Changxin. Effects of Different Doses of Dexmedetomidine on Inflammatory Factors and Postoperative Cognitive Function in Patients Undergoing Gynecologic Laparoscopic Surgery [J]. *China Modern Medicine*,2015,22(30):53-55
- [8] Bao Ning. Effect of Carbon Dioxide Pneumoperitoneum on Postoperative Cognitive Function in Female Patients Undergoing Gynecological Laparoscopy [D]. *China Medical University*,2010
- [9] Qin Xinglong, Huang Chunliu. Effect of Dexmedetomidine on Brain Metabolism and Early Postoperative Cognitive Function in Elderly Patients Undergoing Laparoscopic Surgery [J]. *Jilin Medical Journal*,2016,37(3):552-554
- [10] Qiu Zhenqin, Wang Bingqiong. Effect of Propofol General Anesthesia on Neuron-Specific Enolase (NSE) in Blood Serum, S100B Protein and Cognitive Function of Gerontal Patients [J]. *Journal of Clinical Medicine in Practice*,2016,20(1):39-41
- [11] Li Min, Wang Hao, Miu Changhong, etc. Evaluation of the Accuracy of Target-Controlled Infusion of Remifentanyl for Partial Hepatectomy in Liver [J]. *Shanghai Medical Journal*,2013,36(2):109-113
- [12] Ma Jun. Effect of Remifentanyl on Early Postoperative Cognitive Function in Patients with Cervical Cancer after Radical Resection [J]. *The Practical Journal of Cancer*, 2015, 30(9): 1395-1397
- [13] Xiao Zhanchi, Li Gang, Liu Qiumei. Clinical Observation of Gastrodin Injection Combined with Transcranial Magnetic Stimulation in the Treatment of Vertigo of Vertebral-basilar Artery Insufficiency [J]. *Journal of Emergency in Traditional Chinese Medicine*,2014,23(8):1532-1534
- [14] Sun Xinting, Sun Xiaojing. Effect and Mechanism of Gastrodin on Cognitive Function in Rats with Brain Injury [J]. *Chinese Journal of Rehabilitation Medicine*,2014,29(6):517-520
- [15] Chen Weikang. Pharmacological Action and Clinical Application Progress of Gastrodin Injection [J]. *Strait Pharmaceutical Journal*,2012,24(11):13-16

[16] Tang Heqing, Linlei. The Role of Gastrodin after Cardiopulmonary Bypass [J]. Chongqing Injection in Promoting Early Postoperative Cognitive Medicine,2012,41(19):1933-1935 Recovery in Patients Undergoing Valve Replacement