Journal of Hainan Medical University

http://www.hnykdxxb.com

Effect of general anesthesia combined with epidural anesthesia on the postoperative immune function, stress state and coagulation function in patients with laparoscopic cholecystectomy

Yun−Long Zhao✉

Anesthesiology Department, The First Hospital of Hanbin District Ankang City Shaanxi Province, Ankang 725000, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Laparoscopic cholecystectomy
Epidural anesthesia
Immune function
Stress
Coagulation function

ABSTRACT

Objective: To study the effect of general anesthesia combined with epidural anesthesia on the postoperative immune function, stress state and coagulation function in patients with laparoscopic cholecystectomy. **Methods:** 98 patients undergoing selective laparoscopic cholecystectomy in our hospital between May 2014 and August 2016 were selected and randomly divided into the combined anesthesia group who accepted the general anesthesia combined with epidural anesthesia and the general anesthesia group who accepted the total intravenous anesthesia (n=49), peripheral blood was collected after operation to detect the number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-CD19^+$B cells, serum was collected to detect the levels of stress-related endocrine hormones norepinephrine (NE), cortisol (Cor), insulin (Ins), C-peptide (C-P), free triiodothyronine (FT3), free thyroxine (FT4) as well as coagulation function indexes rostaglandin I2 (PGI2), thromboxane A2 (TXA2), 6-ketone-prostaglandin F1α (6-K-PGI1α) and thromboxane B2 (TXB2). **Results:** The number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-CD19^+$B cells in peripheral blood of combined anesthesia group were significantly higher than those of intravenous anesthesia group (P<0.05); serum NE, Cor, Ins, C-P, FT3, FT4, TXA2 and TXB2 levels of combined anesthesia group were significantly lower than those of intravenous anesthesia group (P<0.05) while PGI2 and 6-K-PGI1α levels were significantly higher than those of intravenous anesthesia group (P<0.05). **Conclusions:** General anesthesia combined with epidural anesthesia can improve the postoperative immune function, stress state and hypercoagulable state in patients with laparoscopic cholecystectomy.

1. Introduction

Cholecystectomy is a normal operation method for clinical treatment of gallbladder disease, and because of its advantages of minimal invasion, laparoscopic cholecystectomy has been increasingly used in clinical treatment[1,2]. In the operation of laparoscopic cholecystectomy, good intraoperative anesthetic effect can reduce the trauma caused by operation and pneumoperitoneum factors, and reduce the immune suppression, stress reaction activation and hemodynamic fluctuations caused by trauma. Total intravenous anesthesia is the traditional anesthesia for laparoscopic cholecystectomy that can inhibit the central nervous system to achieve sedative and analgesic effect. But operation and pneumoperitoneum factors can cause trauma reaction by ascending transmission of somatic nerve and sympathetic nerve, so total intravenous anesthesia alone is unable to effectively block the trauma reaction caused by somatic nerve and sympathetic nerve activation, and the immune suppression, stress reaction

✉Corresponding author: Yun-Long Zhao, Anesthesiology Department, The First Hospital of Hanbin District Ankang City Shaanxi Province, Ankang 725000, China.
Tel: 13319156612
Fund project: Social Development Science and Technology Key Project of Shaanxi Province (No: 2016SF-228).

activation and hemodynamic fluctuations caused by trauma are quite significant. Epidural anesthesia is a common way of intravertebral anesthesia, and the indwelled catheter enables the intraoperative additional medication, which blocks the somatic nerve and sympathetic nerve signal transmission[3,4]. In the following study, the effect of general anesthesia combined with epidural anesthesia on the postoperative immune function, stress state and coagulation function in patients with laparoscopic cholecystectomy was analyzed.

2. Materials and methods

2.1. Research subjects

98 patients who accepted the selective laparoscopic cholecystectomy in our hospital between May 2014 and August 2016 were selected as the research subjects, and the inclusion criteria were as follows: (1) clearly diagnosed with cholelithiasis or cholecystitis, and complying with the indications of selective cholecystectomy; (2) intended to accept selective laparoscopic cholecystectomy; (3) with ASA I-II grade; (4) signing the informed consent. Random number table was used to divide the included patients into combined anesthesia group and general anesthesia group, 49 cases in each group. Combined anesthesia group received general anesthesia combined with epidural anesthesia, including 28 male cases and 21 female cases that were 39–63 years old; general anesthesia group received total intravenous anesthesia, including 31 male cases and 18 female cases that were 37–61 years old. The two groups of patients were not significantly different in general data (P>0.05).

2.2. Anesthesia methods

(1) The anesthesia method of general anesthesia group was as follows: intramuscular injection of 0.1 mg of phenobarbital and 0.5 mg of atropine 30 min before anesthesia, midazolam 3.0 mg, remifentanil 0.25–1.5 μg/kg, succinylcholine 2.0 μg/kg and propofol 2.5 μg/kg for anesthesia induction, and adding remifentanil and succinylcholine according to the intraoperative situation after mechanical ventilation; (2) the anesthesia method of combined anesthesia group was as follows: intramuscular injection of 0.1 mg phenobarbital and 0.5 mg atropine 30 min before anesthesia, then epidural puncture in thoracic 8–9 or 9–10 space, cathetering upward by 3–4 cm, then injection of the mixture of 0.375% ropivacaine and 1% lidocaine, then conducting anesthesia induction, and adding the mixture of 0.375% ropivacaine and 1% lidocaine according to the intraoperative situation through the epidural catheter.

2.3. Peripheral blood index detection methods

24 h after operation, 5 mL of peripheral blood was collected from two groups of patients and anti-coagulated with EDTA to incubate CD3, CD4, CD8, CD16, CD19 and CD56 monoclonal antibody, permeabilization reagent was added, then the incubation continued, the levels of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-CD19^+$B cells were detected in flow cytometer after two times of PBS wash, and the number of above cells per 100 cells were calculated.

2.4. Serum index detection methods

24 h after operation, 5 mL of peripheral blood was collected from two groups of patients, let stand at room temperature for 30 min and centrifuged to separate serum, and enzyme-linked immunosorbent assay kits were used to detect norepinephrine (NE), cortisol (Cor), insulin (Ins), C-peptide (C-P), free triiodothyronine (FT3), free thyroxine (FT4), prostaglandin I2 (PGI2), thromboxane A2 (TXA2), 6-ketone-prostaglandin F1α (6-K-PGI1α) and thromboxane B2 (TXB2) levels.

2.5. Statistical analysis

SPSS20.0 software was used to input and process data, measurement data between two groups was by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Postoperative immune function indexes of two groups of patients

24 h after operation, analysis of the number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and CD3 $CD19^+$B cells in peripheral blood between combined anesthesia group and intravenous anesthesia group is as follows: the number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-CD19^+$B cells in peripheral blood of combined anesthesia group were significantly higher than those of intravenous anesthesia group. Differences in the number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-$ $CD19^+$B cells in peripheral blood were statistically significant between combined anesthesia group and intravenous anesthesia group 24 h after operation (P<0.05) (Table 1).

Table 1

Comparison of postoperative immune function indexes between two groups of patients (n=49, $\bar{x}\pm s$).

Groups	$CD3^+CD4^+CD8^-$	$CD3^+CD4^-CD8^+$	$CD16^+CD56^+$	$CD3^-CD19^+$
Combined anesthesia group	28.76±3.25	22.54±3.31	3.58±0.51	18.92±2.26
Intravenous anesthesia group	21.32±2.89	15.65±1.89	2.31±0.32	11.37±1.48
t	7.201	6.593	7.624	7.991
P	<0.05	<0.05	<0.05	<0.05

3.2. Postoperative stress state indexes of two groups of patients

24 h after operation, analysis of serum stress state indexes NE, Cor, Ins, C-P, FT3 and FT4 between combined anesthesia group and intravenous anesthesia group is as follows: serum NE, Cor, Ins, C-P, FT3 and FT4 levels of combined anesthesia group were significantly lower than those of intravenous anesthesia group. Differences in serum NE, Cor, Ins, C-P, FT3 and FT4 levels were statistically significant between combined anesthesia group and intravenous anesthesia group 24 h after operation (P<0.05) (Table 2).

3.3. Postoperative coagulation function indexes of two groups of patients

24 h after operation, analysis of serum PGI2, TXA2, 6-K-PGI1α and TXB2 between combined anesthesia group and intravenous anesthesia group is as follows: serum PGI2 and 6-K-PGI1α levels of combined anesthesia group were significantly higher than those of intravenous anesthesia group while TXA2 and TXB2 levels were significantly lower than those of intravenous anesthesia group. Differences in serum PGI2, TXA2, 6-K-PGI1α and TXB2 levels were statistically significant between combined anesthesia group and intravenous anesthesia group 24h after operation (P<0.05) (Table 3).

4. Discussion

Laparoscopic cholecystectomy has the feature of minimal invasion, causes small intraoperative injury and is with rapid postoperative recovery[5]. Nonetheless, both operation and pneumoperitoneum factors will cause varying degrees of intraoperative trauma, inhibit the body's immune response, and also activate stress reaction and affect hemodynamics through a variety of endocrine glands[6,7]. In clinical practice, good anesthetic effect can reduce the trauma caused by surgical operation and pneumoperitoneum factors during laparoscopic cholecystectomy. General anesthesia can inhibit the activity of the central nervous system to reduce the surgical trauma of the body, but it doesn't have significant inhibitory effect on the noxious stimulation signal from the ascending transmission of somatic nerve and sympathetic nerve, and its effect is not ideal on improving immune suppression, stress reaction activation and hemodynamic fluctuations caused by trauma[8]. Epidural anesthesia can directly block somatic nerve and sympathetic nerve activity, thereby inhibiting the ascending transmission of noxious stimuli in the somatic nerve and sympathetic nerve[9,10]. Therefore, the combination of general anesthesia and epidural anesthesia can more effectively inhibit the surgical trauma. In order to define the effect of different anesthetic solutions on immune function after laparoscopic cholecystectomy, the immune cell subset levels in the peripheral blood were analyzed in the study, and the results showed that the number of $CD3^+CD4^+CD8^-$T cells, $CD3^+CD4^-CD8^+$T cells, $CD16^+CD56^+$NK cells and $CD3^-CD19^+$B cells in peripheral blood of combined anesthesia group were significantly higher than those of intravenous anesthesia group (P<0.05). This means that general anesthesia combined with epidural anesthesia can reduce the immune suppression caused by laparoscopic cholecystectomy, and the postoperative immune cells are at higher levels.

The trauma caused by operation can not only inhibit the immune function, but can also activate the body's stress response, which is characterized by the abnormal secretion of NE, Cor, Ins, C-P, FT3, FT4 and a variety of other stress-related endocrine hormones[11]. Adrenal gland is an important endocrine gland involved in the stress reaction caused by trauma, the increased sympathetic nerve activity can promote the adrenal medulla to secrete NE, the activation of hypothalamus-pituitary axis can promote the adrenal cortex to secrete Cor, and the NE and Cor can affect the systemic hemodynamics and enhance the body's ability to endure trauma[12]; operation trauma can increase the compensatory blood glucose levels, high blood glucose can stimulate islet β cells to secrete Ins, and the C-P secretion also significantly increases in the synthesis and secretion of Ins[13]; FT3 and FT4 are the pro-metabolism hormones synthesized and secreted by thyroid follicular cells, and they can increase the basal metabolic rate and enhance the body's ability to endure trauma. In the operation of laparoscopic cholecystectomy, good anesthetic effect can enhance

Table 2

Comparison of postoperative stress state function indexes between two groups of patients (n=49, $\bar{x}\pm s$).

Groups	NE (ng/mL)	Cor (ng/mL)	Ins (nmol/L)	C-P (nmol/L)	FT3 (pmol/L)	FT4 (pmol/L)
Combined anesthesia group	42.68±6.62	92.41±10.36	13.51±1.78	0.83±0.11	5.51±0.78	7.61±0.89
Intravenous anesthesia group	67.41±8.29	157.76±17.86	22.36±3.31	1.75±0.20	8.94±0.92	13.25±1.67
t	7.109	8.828	9.581	11.382	7.653	9.035
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Table 3

Comparison of postoperative coagulation function indexes between two groups of patients (pg/mL, n=49, $\bar{x}\pm s$).

Groups	PGI2	TXA2	6-K-PGI1α	TXB2
Combined anesthesia group	103.63±12.57	77.64±9.32	289.76±35.61	157.51±17.86
Intravenous anesthesia group	67.86±8.62	113.26±14.67	214.25±27.65	223.25±26.85
t	7.584	7.112	7.547	8.038
P	<0.05	<0.05	<0.05	<0.05

the body's ability to tolerate surgical trauma, and thus reduce the stress reaction caused by surgical trauma. In order to define the effect of general anesthesia combined with epidural anesthesia on the stress response caused by surgical trauma, postoperative serum levels of stress-related endocrine hormones were analyzed in the study, and the results showed that serum NE, Cor, Ins, C-P, FT3 and FT4 levels of combined anesthesia group were significantly lower than those of intravenous anesthesia group (P<0.05). This means that the general anesthesia combined with epidural anesthesia can reduce the secretion of stress-related endocrine hormones and relieve the extent of the stress response caused by laparoscopic cholecystectomy.

The effect of surgical trauma, postoperative bed rest and stress response on hemodynamics can make the patients in hypercoagulable state, and blood platelet aggregation is significantly aggravated and increases the risk of postoperative thrombotic complications. TXA2 and PGI2 are the important substances to regulate platelet aggregation and vasomotor, the former can contract blood vessels, activate platelet, promote platelet aggregation and accelerate micro-thrombosis, and the latter can dilate blood vessels, inhibit platelet aggregation and reduce the vascular sensitivity to vasoconstrictors. Under physiological conditions, TXA2 and PGI2 are in a state of dynamic balance; surgical trauma and stress can lead to TXA2 and PGI2 imbalance, increase the secretion and activity of TXA2 and inhibit the secretion and activity of PGI2 to lead to hypercoagulable state[14,15]. TXA2 and PGI2 are with short half-life and poor stability in the body, and their metabolites 6-K-PGI1α and TXB2 are relatively stable and can reflect the secretion and activity of TXA2 and PGI2[16]. General anesthesia combined with epidural anesthesia has more ideal intraoperative anesthesia and postoperative anti-stress effect, and further analysis of postoperative blood coagulation function in the study showed that serum PGI2 and 6-K-PGI1α levels of combined anesthesia group were significantly higher than those of intravenous anesthesia group while TXA2 and TXB2 levels were significantly lower than those of intravenous anesthesia group (P<0.05). This means that general anesthesia combined with epidural anesthesia can adjust the balance of TXA2 and PGI2, and reduce the hypercoagulable state after laparoscopic cholecystectomy.

To sum up, it shows that general anesthesia combined with epidural anesthesia has better effect for laparoscopic cholecystectomy than total intravenous anesthesia, and can improve the postoperative immune function, and inhibit the stress state and hypercoagulable state.

References

[1] Rizzuto A, Serra R, Mignogna C, et al. Single incision laparoscopic cholecystectomy in geriatric patients. *Int J Surg* 2016; **35**: 83-87.

[2] Kulen F, Tihan D, Duman U, et al. Laparoscopic partial cholecystectomy: a safe and effective alternative surgical technique in "difficult cholecystectomies". *Ulus Cerrahi Derg* 2016; **32**(3): 185-190.

[3] Ozcan S, Ozer AB, Yasar MA, et al. Effects of combined general anesthesia and thoracic epidural analgesia on cytokine response in patients undergoing laparoscopic cholecystectomy. *Niger J Clin Pract* 2016; **19**(4): 436-442.

[4] Mehta N, Gupta S, Sharma A, et al. Thoracic combined spinal epidural anesthesia for laparoscopic cholecystectomy in a geriatric patient with ischemic heart disease and renal insufficiency. *Local Reg Anesth* 2015; **2**(8): 101-104.

[5] Al Rawahi A, Al Azri Y, Al Jabri S, et al. Successful laparoscopic management of duplicate gallbladder: a case report and review of literature. *Int J Surg Case Rep* 2016; **21**: 142-146.

[6] Velidedeoglu M, Arikan AE, Uludag SS, et al. Clinical application of six current classification systems for iatrogenic bile duct injuries after cholecystectomy. *Hepatogastroenterology* 2015; **62**(139): 577-584.

[7] Lirici MM, Tierno SM, Ponzano C. Single-incision laparoscopic cholecystectomy: does it work? A systematic review. *Surg Endosc* 2016; **30**(10): 4389-4399.

[8] Singh RK, Saini AM, Goel N, et al. Major laparoscopic surgery under regional anesthesia: A prospective feasibility study. *Med J Armed Forces India* 2015; **71**(2): 126-131.

[9] Bilgi M, Alshair EE, Göksu H, et al. Experience of laparoscopic cholecystectomy under thoracic epidural anaesthesia: retrospective analysis of 96 patients. *Turk J Anaesthesiol Reanim* 2015; **43**(1): 29-34.

[10] Hajong R, Khariong PD, Baruah AJ, et al. Laparoscopic cholecystectomy under epidural anesthesia: a feasibility study. *N Am J Med Sci* 2014; **6**(11): 566-569.

[11] Sidiropoulou I, Tsaousi GG, Pourzitaki C, et al. Impact of anesthetic technique on the stress response elicited by laparoscopic cholecystectomy: a randomized trial. *J Anesth* 2016; **30**(3): 522-525.

[12] Pędziwiatr M, Pisarska M, Matłok M, et al. Randomized clinical trial to compare the effects of preoperative oral carbohydrate loading versus placebo on insulin resistance and cortisol level after laparoscopic cholecystectomy. *Pol Przegl Chir* 2015; **87**(8): 402-408.

[13] Floros T, Philippou A, Bardakostas D, et al. The growth endocrine axis and inflammatory responses after laparoscopic cholecystectomy. *Hormones (Athens)* 2016; **15**(1): 73-80.

[14] del Campo M, Sagredo A, del Campo L, et al. Time-dependent effect of orchidectomy on vascular nitric oxide and thromboxane A2 release. Functional implications to control cell proliferation through activation of the epidermal growth factor receptor. *PLoS One* 2014; **9**(7): e102523.

[15] Jeong IS, Cho HJ, Cho JG, et al. Influence of thromboxane A2 on the regulation of adenosine triphosphate-sensitive potassium channels in mouse ventricular myocytes. *Korean Circ J* 2016; **46**(4): 562-568.

[16] Lian W, Zhang H, Wang K, et al. Varying levels of 6-keto-prostaglandin F1α and thromboxane B2 in serum and endothelialization and hyperplasia in small-diameter grafts seeded with $CD34^+$ bone marrow cells in canines. *Exp Ther Med* 2014; **7**(5): 1123-1129.