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Original Article

Effects of total intravenous anesthesia and combined general-epidural anesthesia on erythrocyte immunity in patients undergoing laparoscopic resection of ovarian tumor

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Abstract: Objective: To analyze the effects of two different anesthesia methods, total intravenous anesthesia (IVA) and combined general-epidural anesthesia (EIVA), on erythrocyte immunity in patients undergoing laparoscopic resection of ovarian tumor. Methods: A total of 100 patients who were prepared for the laparoscopic resection of ovarian tumor in our hospital were recruited as subjects. The patients either received IVA or EIVE for the surgery in a random way. Samples of venous blood were collected across different time points which were before (T1) and 30 min after (T2) anesthesia, 1 h intra-operation (T3), 24 h (T4), 48 h (T5) and 72 h (T6) after operation, and the changes of erythrocyte immune functions were measured, including the rate of red blood cell C3b receptor rosette (RRCR), rate of red blood cell immune complex rosette (RRICR), rate of red blood cell circulating immune complex rosette (RRCICR), and rate of tumor red blood cell rosette (RTRR). Results: Similar variation patterns were observed in both groups regarding the values of RRCR, RRICR, RRCICR and RTRR before and after anesthesia; however, from T2 to T5, the levels of these indices in IVA group decreased more than those in EIVA group ($P<0.05$). Conclusion: Anesthesia could cause harm to the erythrocyte immunity in patients, however, compared with IVA, the damage by EIVA appeared to less.

Keywords: Laparoscopic resection of ovarian tumor, anesthesia, erythrocyte immunity

Introduction

Anesthesia methods including general anesthesia, combined general-epidural anesthesia can all be applied in the gynecologic laparoscopic surgery clinically. In recent years, the effects of different kinds of anesthesia on the immune system have been gaining attention. For example, it was reported that anesthesia could induce the stress response during perioperative period and suppress the cell-mediated immunity [1]. Different types of anesthesia could make different levels of impacts on the functions of immunoglobulin G, complement C3, C4, and affect the release of cytokines, such as interleukin-4 [2]. The idea of erythrocyte immunity was first proposed by Siegel in 1981, and in those studies, the impacts of various diseases and trauma on the erythrocyte immunity were investigated. However, there were only few animal studies regarding the effects of anesthesia on the immune function of red blood cell (RBC) [3].

RBC has many components that are related to the immunity, such as CR1, CR3, CD58, CD59, IL-8R, DAF, SOD, creating a system of its own. The erythrocyte immunity is mainly based on CR1, and can be impaired if the number of CR1 decreases or if there is a structural change. Both congenital factors and acquired factors (such as surgery, trauma, infection, anemia, oxygen free radicals, and erythrocyte senescence) can bring about functional defect of CR1 in RBC. Currently, there are three major indices that can reflect RBC CR1 adhesion activity, which are rate of RBC C3b receptor rosette (RRCR), rate of RBC immune complex rosette (RRICR), rate of RBC circulating immune complex rosette (RRCICR), and rate of tumor RBC rosette (RTRR).

Table 1. Comparison of patients' general information

Data	IVA	EIVA	χ^2/t	P
Age (year)	28.6±6.3	31.5±7.2	1.3061	0.3531
Tumor type				
Teratoma of ovary (count)	26	27	0.0401	0.8412
Ovarian serous cystadenoma (count)	10	10	0	1
Simple ovarian cyst (count)	9	10	0.0650	0.7988
Mucinous cystadenoma (count)	5	3	0.5435	0.4610
Anesthesia time (min)	42.6±10.2	43.8±11.6	0.5216	0.4632
Preoperative ASA rating	I-II	I-II	0.6321	0.1254
Depth of anesthesia	69.2	58.1	0.3261	0.8541

Some scholars found that both general and local anesthesia could weaken the erythrocyte immune functions in tumor-bearing rats, while the level of damage caused by the former one was greater [4]. Therefore, this study aimed to explore the effects of these two types of anesthesia on the erythrocyte immunity clinically, using patients who received laparoscopic resection of ovarian tumor in our hospital as subjects.

Materials and methods

General information

The study was approved by the Ethics Committee in the hospital and informed consents were obtained by the participants. One hundred patients who received laparoscopic resection of ovarian tumor in our hospital from June 2015 to January 2017 were selected as subjects.

Inclusive criteria: Adult female who suffered from malignant ovarian tumor without distant metastasis and voluntarily participated in our study; laparoscopic surgery was conducted for treatment.

Exclusion criteria: Patients who couldn't undergo surgery or receive anesthesia; patients had endocrine dysfunction; patients had systemic infection; patients had circulatory disease; patients had contraindication for anesthesia; patients who were not willing to participate in the study; patients who were receiving perioperative blood transfusion. According to the sortition randomization method, subjects were divided into two groups, total intravenous anesthesia (IVA) group and combined general-epidural anesthesia (EIVA) group, with 50 cases in each group.

Methods

Before entering the operation room, patients in both groups were intramuscularly injected with 0.5 mg atropine (Jiaozuo Furuitang Pharmaceutical Co., Ltd.) and 0.1 g phenobarbital sodium (Tianjin Pharmaceutical Group Xinzheng Co., Ltd.). After that, the venous access was established and sodium lactate Ringer's solution was transfused.

Patients in IVA group received intravenous infusion of 1.5 mg/kg propofol (Nhwa Pharma Corporation), 5 μg/kg fentanyl, 0.5 mg/kg Midazolam (Nhwa Pharma Corporation) and 0.8 mg/kg Atracurium. Following induction of anesthesia, the endotracheal intubation was performed while anesthesia was maintained by pump infusion of Propofol at a dose of 6-10 mg/(kg*h) and intravenous injection of Atracurium and fentanyl.

Patients in EIVA group received epidural injection of 3 ml (10 g) lidocaine at T12-L1 (Fujian Jinshan biological pharmaceutical Co., Ltd., each gram contains 25 mg prilocaine and 25 mg lidocaine). The induction of anesthesia was the same as the one in IVA group, followed by the endotracheal intubation. Prior to the operation, a continuous infusion of 3-6 mg/(kg*h) Propofol was conducted and 6-8 ml/h ropivacaine (Hebei Yipin Pharmaceutical Co., Ltd.) was injected into the epidural space of the patient.

Patients in both groups were connected to the depth-of-anesthesia monitor and the values of Bispectral index were maintained at 40-60.

Outcome measures

In order to measure the changes of erythrocyte immune functions, the venous blood samples were collected at six time points, which were before (T1) and 30 min after (T2) anesthesia, 1 h intra-operation (T3), 24 h (T4), 48 h (T5) and 72 h (T6) after operation. The rosette tests were performed to assess the erythrocyte immunity (test items include RRCR, RRICR, RRCICR, and RTRR).

Table 2. General physiological indices

Indicator	Group	T1	T2	T3	T4	T5	T6
MAP (mmHg)	EIVA	85.3±11.2	82.5±9.6	87.5±9.6	85.6±10.5	87.2±5.6	86.9±6.2
	IVA	85.2±11.6	84.2±10.7	86.3±11.0	85.1±11.5	86.5±9.7	87.1±5.9
HR (times/min)	EIVA	84.6±14.8	77.5±12.6	81.5±12.6	84.2±12.6	84.8±10.2	84.6±12.7
	IVA	85.1±12.6	70.8±11.6	82.8±15.6	84.7±10.5	85.1±12.6	84.1±11.7
RR (times/min)	EIVA	16.8±4.1	16.1±4.2	16.2±3.6	15.8±4.5	16.7±4.2	16.8±3.9
	IVA	16.5±3.9	16.4±4.2	16.2±3.7	15.9±4.8	16.7±3.8	16.5±4.2

Table 3. Changes of erythrocyte immune function before and after anesthesia

Index	Group	T1	T2	T3	T4	T5	T6
RRCR	EIVA	18.5±6.5	15.6±4.2$^{*,\#}$	14.4±4.1$^{*,\#}$	13.2±3.5$^{*,\#}$	12.3±3.2$^{*,\#}$	17.4±3.9
	IVA	18.8±7.5	16.3±4.3*	11.3±3.7*	10.4±4.2*	9.4±4.3*	17.3±3.9
RRICR	EIVA	11.4±5.1	9.8±3.2$^{*,\#}$	9.2±2.5$^{*,\#}$	6.9±1.3$^{*,\#}$	8.4±1.3$^{*,\#}$	10.8±2.8
	IVA	12.0±5.2	8.3±2.6*	7.6±2.2*	5.7±1.4*	7.1±1.3*	10.2±2.4
RRCICR	EIVA	8.9±1.4	6.3±1.5*	6.0±1.0*	6.3±1.9$^{*,\#}$	6.5±1.5$^{*,\#}$	7.0±1.2
	IVA	9.2±1.5	7.5±1.6$^{*,\#}$	6.8±1.1$^{*,\#}$	7.2±1.4*	7.5±1.6*	7.9±1.1
RTRR	EIVA	42.6±11.3	39.2±9.7$^{*,\#}$	37.8±8.2$^{*,\#}$	35.7±9.8$^{*,\#}$	37.0±7.2$^{*,\#}$	41.7±10.6
	IVA	43.2±12.5	34.8±8.6*	33.2±9.2*	30.3±8.5	33.7±8.9*	40.8±10.4

Notes: Compared with T1, $^{*}P<0.05$; compared with IVA group, $^{\#}P<0.05$.

Method for determining the erythrocyte immunity [5] was as follows: 10 ml venous blood was collected at each time point and stored in test tube containing nutritive medium. RBCs were diluted to a suspension of $1.2*10^{7}$/ml and saved for later use. The C3b sensitized freeze-dried yeast was dissolved in 1 ml normal saline. Meanwhile, the normal saline only was added into each tube (0.05 ml) and frozen for reserve. After that, the prepared C3b receptor sensitized freeze-dried yeast suspension (0.05 ml) was added, followed by mixing, smearing, incubating and dyeing. Two hundred RBCs were counted under oil immersion lens. The result was positive if more than two yeasts were combined. Then, the value of RRCR was calculated. Methods for testing other indices were the same as the method for RRCR. All the reagents (complement sensitized yeast assay kits and complement insensitive yeast assay kits) and test services were provided by Beijing LaBEST Biotechnology Co., Ltd.

Statistical analysis

The database was created by Microsoft Excel, and SPSS 19.0 statistical software was used for data analysis. The measurement data was expressed as the mean ± standard deviation; comparisons between groups were conducted by t test. The count data was expressed as percentage and the difference between groups was compared by chi-square test. A value of $P<0.05$ was considered as statistically significant.

Results

General information

There was no intergroup difference in the general information (P>0.05, **Table 1**).

General physiological indices

There was no significant difference in the general physiological indices including mean arterial pressure (MAP), heart rate (HR) and respiratory rate (RR) between two groups as was shown in **Table 2**.

Changes of erythrocyte immune function before and after anesthesia

Before anesthesia, there was no significant difference in indices including RRCR, RRICR, RRCICR and RTRR between two groups. However, after anesthesia, all of the four indices showed the same pattern of change, i.e. declined first and recovered later. Differences in

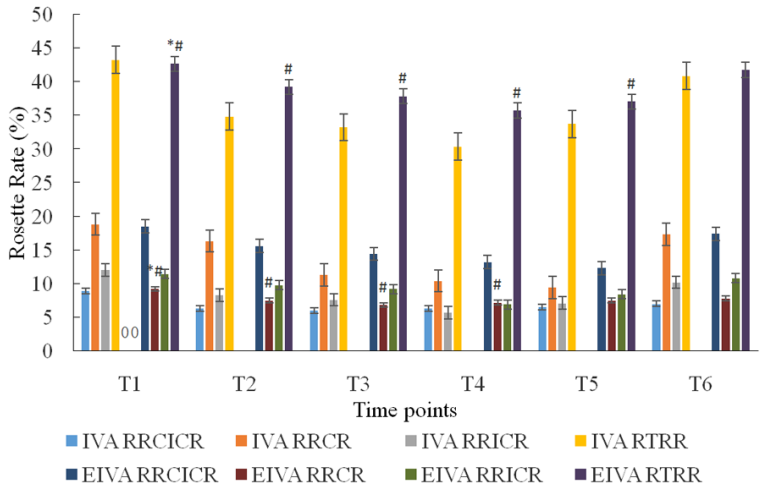

Figure 1. RRCR, RRICR, RRCICR, RTRR before and after anesthesia.

these values between T2 and T1 were statistically significant (P<0.05). Moreover, values of RRCR reduced to the lowest level at T5 and returned to normal at T6. The lowest values of RRICR, RTRR were at T4, while the lowest values of RRCICR were at T3, followed by a gradual recovery to normal. From T2 to T5, intergroup differences in the values of RRCR, RRICR RRCICR and RTRR were significant (P<0.05), with a more significant reduction occurred in IVA group. See **Table 3** and **Figure 1**.

Discussion

Previous studies have found that RBC plays an important role in body's immune system, as it can recognize and remove circulating immune complexes, as well as contributes to the anti-tumor and anti-infection immunity [6]. The erythrocyte immune system is not only involved in the auto-regulation function, but is also regulated by the neuroendocrine system [7]. Trauma and anesthesia would affect the erythrocyte immunity, just like they would harm the leukocyte immune system, and many people believed that anesthesia could inhibit the immune function [8]. However, there were few studies regarding the effects of different anesthesia methods on the erythrocyte immunity.

In this study, patients undergoing laparoscopic resection of ovarian tumor were chosen as subjects. Factors that may affect the outcome, such as surgical trauma, age, infection, erythrocyte senescence were excluded. We found that there was no significant difference in the level of RRCR, RRICR, RRCICR and RTRR between two groups prior to the operation. After anesthesia, these indicators presented similar trends of variation, i.e., declined first and recovered afterwards. Moreover, the values of these indicators in both groups decreased significantly at T2 as compared to T1. This might be due to the fact that the regulating function of RBC became disordered after anesthesia, and the effects of inhibitory factors were enhanced, which weakened the immune adherence function [9]. The RRCR value was reduced to the lowest level at T5 and returned to normal at T6, while values of RRICR and RTRR decreased to the lowest level at T4, and RRCICR decreased to the lowest level at T3, followed by a gradual recovery. In addition, the reduction of these indices in IVA group was greater than those in EIVA group. All of these findings suggested that both anesthesia methods could cause the primary erythrocyte immunity decrease. However, compared with IVA, the impact made by EIVA was less severe [10]. Our results are consistent with the findings in the previous reports that EIVA can have the advantages of both general anesthesia and epidural anesthesia [11], and cause less suppression of patients' immune functions, especially cellular immunity [12].

This study showed that the erythrocyte immunity in patients gradually returned to normal 72 h after operation, which indicated that the immune function of RBC can be reversible. This finding suggested the necessity to enhance the anti-infection treatment for patients with malignant tumor, and to improve their immune functions. Compared to IVA, EIVA appeared to have less effect on erythrocyte immunity. The RBC immune system is not just self-regulated, but is also regulated by neuroendocrine system [13]. Like anesthesia and surgical trauma would cause harm to the white blood cell immune system [14, 15], they would also interfere with the erythrocyte immunity to some extent by affecting the internal environment and neuro-system [16].

Previous studies have revealed that the activity of C3b receptor on erythrocyte membrane surface and the immune complex rosette (ICR) which indicates the ability to bind immune complexes are both important indices for erythrocyte immunity [17]. If these two values decrease, it means there is primary erythrocyte immunity decrease [18]. However, if the activity of C3b receptors on erythrocyte membrane surface increases while the level of ICR decreases, it means that RBCs are adhering with too many immune complexes, and there is secondary erythrocyte immunity decrease [19]. In this study, since the level of ICR and the activity of C3b receptors both declined, it was suggested that IVA could lead to the primary erythrocyte immunity decrease.

There were still some limitations in the study. First, the surgical stress stimulation could affect the erythrocyte immunity, but the individual differences in this area were not excluded from the study [20]. Second, there hadn't been many studies on the erythrocyte immune system, and the mechanism of how anesthesia affects immune function of RBC remained to be further investigated.

In conclusion, anesthesia could cause harm to erythrocyte immunity, but the damage by EIVA appeared to be less as compared to that by IVA.

Disclosure of conflict of interest

None.

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