Int J Clin Exp Med 2015;8(6):9862-9868
www.ijcem.com /ISSN:1940-5901/IJCEM0008692

Original Article

Effects of epidural preemptive analgesia on stress reaction in retroperitoneal laparoscopic adrenalectomy surgery: a randomized controlled study

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Received April 1, 2015; Accepted June 2, 2015; Epub June 15, 2015; Published June 30, 2015

Abstract: Objective: To compare the effects of general anesthesia combined with epidural preemptive analgesia with general anesthesia on stress reaction in the retroperitoneal laparoscopic surgery. Methods: Forty patients with adrenal tumors undergoing retroperitoneal laparoscopic surgeries were randomly assigned into general anesthesia combined with epidural preemptive analgesia group (GE) and general anesthesia group (G). Each group had 20 cases. In the GE group, before the induction of general anesthesia, T10-T11 epidural puncture was performed and 0.2% bupivacaine 5-10 ml was injected to maintain the anesthesia level at T4. In the G group, normal saline was injected as control. After entry into the operation room (X0), before surgery (X1), 30 min after pneumoperitoneum (X2), 60 min after pneumoperitoneum (X3), 10 min after extubation (X4), the mean arterial pressure (MAP) and heart rate (HR) were recorded. The concentration of plasma endothelin (ET) and calcitonin gene-related peptide (CGRP) were detected. Meanwhile, isoflurane inhalation MAC and intervention situations were recorded. Results: At X1-X3, MAP in the GE group was significantly lower than that in the G group ($P < 0.05$). At X2-X4 HR in two groups was significantly faster than at X1 ($P < 0.05$). At X4 HR in the GE group was significantly lower than that in the G group ($P < 0.05$). At X3 and X4, ET and CGRP were significantly lower than those in the G group ($P < 0.05$). At X2 and X3, ET in the GE group was significantly higher than that at X1 ($P < 0.05$). At X3, CGRP in the GE group was significantly higher than that at X1 ($P < 0.05$). At X2, X3 and before pneumoperitoneum, isoflurane MAC in the GE group was significantly lower than that in the G group ($P < 0.05$). At X2 and X3, isoflurane MAC in two groups was significantly higher than that during pneumoperitoneum ($P < 0.05$). Conclusion: Compared with general anesthesia, general anesthesia combined with epidural preemptive analgesia can effectively alleviate patients' stress reaction under retroperitoneal laparoscopic surgery.

Keywords: Retroperitoneal laparoscopic surgery, preemptive analgesia, stress reaction

Introduction

Stress is a series of non-specific neural-endocrinal response caused by stressors like surgeries or traumas on body. Appropriate stress reaction helps the body resist external damage. However, if the reaction is unbalanced or intense, it will result in sympathetic hyperfunction which causes tachycardia, hypertension, myocardial ischemia, arrhythmia and other pathological changes and increases risks in surgery among the elderly or patients with cardiovascular diseases.

Because of its minimal invasiveness, less postoperative pain, faster recovery, shorter hospital stay and so on, the retroperitoneal laparoscopic surgery has been widely used in Urinary Surgery Department. However, in the surgery CO_2 increases the intra-abdominal and intrathoracic pressure, which leads to cardiac output decrease and increases sympathetic activity in a reflex. On the other hand, CO_2 accumulation in the body leads to hypercapnia, which indirectly stimulates aortic body chemosensory organs and carotid sinus, increasing the concentration of plasma catecholamines, cortisol and vasopressin [1, 2]. Therefore, the CO_2 pneumoperitoneum intensifies the stress reaction, manifested as blood pressure rising and heart rate accelerating. Especially in the fast inflation stage of CO_2 pneumoperitoneum, there is a significant increase in the concentration of MAP, HR, plasma NE, E, Cor [3, 4]. Some scholars believed that the retroperitoneal laparoscopic surgery could only be regarded as "micro-channel" operation rather than minimally invasive surgery [5]. In previous studies it has been proved safe and effective that epidural preemptive analgesia reduces the intensity of the stress reaction in the retroperitoneal laparoscopic surgery [4]. But cases of adrenal tumors were excluded. In the adrenal tumorectomy, it's unavoidable to operate on the adrenal gland, which may induce the sudden massive release of catecholamines, cortisol and other stress hormones and intensify the body stress reaction. Whether epidural preemptive analgesia could reduce the intensity of stress reaction in retroperitoneal laparoscopic adrenalectomy in a larger degree compared to simple general anesthesia was rarely reported. This study was conducted to investigate it.

Data and methods

General data

Forty patients of adrenal tumors (adrenal adenoma, adrenal cysts, adrenal carcinoma) with ASA grade I to II received retroperitoneal laparoscopy. Patients with pheochromocytoma, unsatisfactory blood pressure control (systolic pressure over 160 mmHg one week before surgery), severe respiratory or cardiac diseases, coagulation disorders or epidural puncture contraindications were excluded. All patients signed preoperative anesthesia consent forms and the study was approved by the research ethics committee of the hospital. All cases were numbered according to the operation time and assigned into two groups with a random number table: epidural preemptive analgesia combined with general anesthesia group (GE group) and general anesthesia group (G group). Grouping information was recorded by a designated anesthesia nurse.

Equipment and reagents

Anesthesia machine: Datex-Ohmeda Aestiva/5; vital signs monitor: Datex-Ohmeda s/5; arterial pressure measurement module: Biosensors international DPT-248; refrigerated centrifuge: DDL-5; Smart γ radiation meter: SN-695B; iodine [125I] endothelin (ET) radioimmunoassay kit (100T) and iodine [125I] calcitonin gene-related peptide (CGRP) radioimmunoassay kit (100T) were purchased from Beijing Purevalley Biotechnology company.

Preemptive epidural analgesia

No preoperative medications were given. Regular vital signs like heart rate, NIBP, SpO_2 were monitored when patients entered the operation room. Ringer's lactate 500 ml was administered via peripheral veins to expand the blood volume. All patients were first given T10-T11 epidural punctures, a catheter was inserted 3 cm towards the head and experimental agents 5 ml (provided by the anesthesia nurse in charge of grouping: 0.2% Bupivacaine for GE group, normal saline for G group) were prepared. Afterwards the patient was closely monitored for 10 min. Patients had stable respiration and circulation, reported no lower limb movement disorder, palpitations, cold sweats and presented no altered mental status. If analgesia on the T4 level did not occur, the prepared agents 5-10 ml were injected into the epidural space based on the weight of patients. Otherwise epidural injection was cancelled and patients were excluded. Last, midazolam 0.03 mg/kg was given intravenously and ABP was monitored through catheters placed in the radial artery of the non-surgical side.

General anesthesia

After intravenous use of fentanyl 6 ug/kg, etomidate 0.3 mg/kg and atracurium 6 mg/kg for induction, intubation and mechanical ventilation were employed. The tidal volume and respiratory rates were adjusted as needed to maintain $PETCO_2$ at 40~50 mmHg, PawP < 30 cm H_2O. The lateral recumbent head-down position was taken and anesthesia was started 10 min later. The pneumoperitoneum pressure was set to 12 cm H_2O. Inhalation of isoflurane (MAC) was used to maintain anesthesia depth, and atracurium 25 mg/h was continuously pumped intravenously to maintain muscle paralysis. When the laparoscopic operation was over, pneumoperitoneum was stopped when the atracurium infusion was stopped. The isoflurane inhalation was stopped when the surgery was over, the oxygen flow was adjusted to 10 L/min. The patient turned to supine position. When the patient became awake, spontaneous breathing tidal volume > 6 ml/kg, respi-

Table 1. General information (mean ± SD)

group	case	Sex (male/female)	hypertension (case)	Age (years)	Weight (kg)	tumor size (cm)	operation time (min)	pneumoperitoneum time (min)	extubation time (min)
GE	20	10/10	11	50.7 ± 11.0	66.3 ± 10.2	5.6 ± 2.0	140.1 ± 40.1	119.0 ± 29.1	12.3 ± 6.9[*]
G	20	12/8	9	52.1 ± 12.0	68.4 ± 8.4	5.0 ± 1.8	134.9 ± 39.5	109.1 ± 40.9	17.3 ± 7.2
P value				0.703	0.493	0.340	0.686	0.383	0.030

[*]Compared with the G group, $P < 0.05$.

Table 2. MAP and HR comparison (mean ± SD)

Indicators	Group	After entry into OR	Before surgery	30 min pneumoperitoneum	60 min pneumoperitoneum	10 min after extubation
MAP (mmHg)	GE	92.1 ± 8.4	79.0 ± 10.4[*,#]	88.5 ± 12.0[*,⊿]	91.2 ± 13.1[*,⊿]	88.2 ± 11.8[⊿]
	G	95.6 ± 8.3	86.6 ± 8.5[#]	96.7 ± 12.6[⊿]	99.6 ± 11.8[⊿]	91.8 ± 14.2[⊿]
P value		0.188	0.015	0.041	0.040	0.396
HR (bpm)	GE	83.1 ± 11.4	71.8 ± 9.3[#]	83.5 ± 9.6[⊿]	85.5 ± 10.9[⊿]	82.5 ± 10.2[*,⊿]
	G	80.4 ± 9.5	75.4 ± 8.4[#]	87.4 ± 10.0[#,⊿]	89.3 ± 12.5[#,⊿]	89.7 ± 10.3[#,⊿]
P value		0.430	0.083	0.221	0.306	0.033

[*]Compared with the G group, $P < 0.05$; [#]compared with after entry into OR, $P < 0.05$; [⊿]compared with before the surgery, $P < 0.05$.

Table 3. ET and CGRP comparison (mean ± SD)

indicator	group	after entry into OR	before surgery	30 min pneumoperitoneum	60 min pneumoperitoneum	10 min after extubation
ET (pg/ml)	GE	53.2 ± 11.0	46.0 ± 9.6[#]	53.6 ± 11.2[*,⊿]	54.3 ± 12.8[*,⊿]	52.6 ± 12.3[*]
	G	51.0 ± 10.8	48.6 ± 8.5	61.1 ± 11.2[#,⊿]	63.1 ± 11.4[#,⊿]	60.1 ± 10.4[#,⊿]
P value		0.534	0.376	0.041	0.027	0.044
CGRP (pg/ml)	GE	30.3 ± 7.3	26.9 ± 7.2	31.0 ± 10.4	32.7 ± 10.1[*,⊿]	30.7 ± 9.0[*]
	G	31.1 ± 8.5	29.2 ± 8.2	36.5 ± 9.7[⊿]	40.3 ± 10.4[#,⊿]	37.6 ± 11.9[⊿]
P value		0.753	0.461	0.09	0.024	0.046

[*]Compared with the G group, $P < 0.05$; [#]after entry into OR, $P < 0.05$; [⊿]compared with before the surgery, $P < 0.05$.

Table 4. Intraoperative MAC comparison (mean ± SD)

Indicators	group	before pneumoperitoneum	30 min pneumoperitoneum	60 min pneumoperitoneum	After surgery
MAC	GE	0.67 ± 0.37*	1.05 ± 0.45*,⊿	1.23 ± 0.61*,⊿	0.18 ± 0.10*,⊿
	G	1.23 ± 0.53	1.69 ± 0.64⊿	1.61 ± 0.52⊿	0.37 ± 0.22⊿
P value		0.000	0.001	0.043	0.001

*Compared with the Group, P < 0.05; ⊿Compared with before pneumoperitoneum, P < 0.05.

Table 5. Interventions comparison

Medications	group	before pneumoperitoneum	30 min pneumoperitoneum	60 min pneumoperitoneum	10 min after extubation
nicardipine (case)	GE	0	3	3	6
	G	0	6	5	8
P value		0.449	0.693	0.741	
phenylephrine (case)	GE	3	0	0	0
	G	1	0	0	0
P value					0.605
esmolol (case)	GE	0	2	3	7
	G	0	4	5	10
P value		0.661	0.693	0.523	
atropine (case)	GE	3	0	0	0
	G	1	0	0	0
P value					0.605

ratory rate > 8/min, choking and swallowing reflex recovered, the endotracheal tube was removed.

Blood pressure and heart rate interventional measures

The concentration of isoflurane inhaled was adjusted to control the systolic blood pressure at 110~140 mmHg. When the blood pressure was over this range for more than 1 min, 50% increase or decrease of the isoflurane concentration was adjusted immediately. After 3 min it was re-evaluated. If the blood pressure fluctuated greatly, over 180 mmHg, intravenous nicardipine 0.5 mg was used; below 80 mmHg, intravenous phenylephrine 100 μg was used. Intravenous use of esmolol 20 mg was adopted when HR > 120 bpm; When HR < 55 bpm, intravenous atropine 0.25 mg was used.

Indicators monitored

General conditions of patients (sex, age, body weight, history of hypertension, tumor size, pneumoperitoneum time, extubation time, etc.) were recorded. Mean arterial pressure (MAP), heart rate (HR), plasma ET, CGRP concentration isoflurane MAC values were recorded after entering the OR, before surgery, 30 min after pneumoperitoneum, 60 min after pneumoperitoneum, 10 min after extubation. The total amount of medications used for blood pressure and heart rate adjustment were recorded. Plasma ET and CGRP concentrations were detected by radioimmunoassay.

Statistical analysis

The SPSS13.0 software was employed. The measurement data were presented as mean ± standard deviation. Data between different groups were compared using a test. At different time points the differences between groups and within groups were compared using analysis of variance. Count data were compared with chi-square test. P < 0.05 was considered statistically significant.

Results

General information comparison

No statistical difference was found between two groups in sex, age (27-72 years), body weight (49-90 kg), hypertension history, tumor size (1.7-10.4 cm), operation time, pneumoperitoneum time. The extubation time was shorter in the GE group than that in the G group ($P < 0.05$) **Table 1**.

Blood pressure and heart rate comparison

Intraoperatively MAP was significantly lower in the GE group than that in the G group and the difference was statistically significant ($P < 0.05$). MAP was significantly lower before the surgery and elevated after the establishment of pneumoperitoneum for both groups. However, the difference was not statistically significant compared with the MAP measured after entry into the OR. Intraoperatively, HR in the GE group was reduced compared with that of the G group. The difference was statistically significant after extubation ($P < 0.05$). HR was reduced before the surgery and significantly elevated after the establishment of pneumoperitoneum ($P < 0.05$) **Table 2**.

Plasma ET and CGRP levels comparison

Intraoperative plasma ET and CGRP levels were significantly lower in the GE group than those in the G group and the difference was statistically significant ($P < 0.05$). ET and CGRP levels in both groups dropped to the lowest before the surgery and significantly increased after the pneumoperitoneum establishment. Compared those after entry into OR, differences existed in the G group at some time points ($P < 0.05$). **Table 3**.

Anesthesia depth comparison between two groups

At all time points, the MAC concentration of isoflurane inhaled was significantly lower in the GE group than that of the G group ($P < 0.05$) and significantly increased after the pneumoperitoneum establishment ($P < 0.05$) **Table 4**.

Interventions comparisons

Cases with the esmolol and nicardipine interventions in the GE group were significantly less than those of the G group. But the difference was statistically insignificant. Cases with the atropine, phenylephrine interventions in the GE group were significantly more than those of the G group. No statistical difference was found **Table 5**.

Discussion

Although laparoscopic surgery is minimally invasive, CO_2 pneumoperitoneum could increase the stress response. The main mechanisms [6] include that ① hypercapnia stimulates the chemoreceptors of the carotid sinus and aortic body thus elevating the plasma concentrations of catecholamines, antidiuretic hormone and cortisol; ② during pneumoperitoneum mechanical stimulation causes abdominal muscles stretch pain; ③ pneumoperitoneum increases intrathoracic pressure and intra-abdominal pressure, obstructs the venous return, reduces cardiac output and increases the sympathetic activity in a reflex. Therefore, during laparoscopic surgeries the stress reaction intensity is correlated with the CO_2 absorption levels and cross-peritoneal pressure. Compared with the peritoneal cavity, the retroperitoneal cavity is enriched with blood vessels, fat tissue. Thus, the CO_2 absorption is more significant. The laparoscopic urological surgery is more complicated than the simple laparoscopic cholecystectomy. Usually pneumoperitoneum lasts over 1h. In the adrenal surgery the stretch and squeeze increase the release of catecholamines [7]. Therefore, the stress response in retroperitoneal laparoscopic adrenal surgery is much stronger.

General anesthesia can provide a safe airway for laparoscopic surgeries and control the discharge of CO_2. Besides, it confers good muscle relaxation and a clear operative field [8, 9]. However, simple general anesthesia can only suppress the limbic system of the cerebral cortex and the projection system of the hypothalamus to the cerebral cortex. It cannot block the increased release of hormones by the pituitary and adrenal medulla stimulated by the surgical noxious stimuli. Therefore the stress response is significant [10-12]. The epidural anesthesia can effectively block the nerve conduction pathway of noxious stimulations [13, 14]. Thus, general anesthesia combined with preemptive epidural analgesia can provide a good surgical environment and a lighter stress status for retroperitoneal laparoscopic surgeries.

ET and CGRP in plasma are powerful endogenous factors to maintain arterial systolic and diastolic pressure. Anesthesia and surgery can cause them to rise. Thus, they are used as important indicators to evaluate intraoperative stress intensity [15-18]. Plasma has low levels of ET and CGRP which are rapidly eliminated with a short half-life. Therefore, they are rapid and sensitive indicators appropriating for intraoperative evaluation of the stress intensity [19, 20].

This study attempted to exclude the influence of preoperative blood pressure, tumor size on the results. **Table 1** showed that these disturbances had been effectively controlled. Because it was difficult to evaluate the impacts of tumors, this study employed randomization for grouping, screened cases (satisfactory blood pressure control one week before surgery and excluding pheochromocytoma), observed and analyzed the blood pressure after entry into the operation room, heart rate, ET, CGRP. For this study mainly focused on effects of different methods of anesthesia on the patient stress reaction, by screening patients (excluding the respiratory and heart diseases), and intraoperative controlling the $PETCO_2$ excluded the influence of CO_2 absorption differences on results.

In this study, we found that MAP, HR, ET and CGRP were all significantly elevated after the establishment of pneumoperitoneum and continuously increased during pneumoperitoneum, indicating that after pneumoperitoneum, the stress reaction became intensified. Indicators in the GE group were lower than those in the G group, suggesting that the stress reaction control in the GE group was more satisfactory than those in the G group. Compared with the G group, in the GE group intraoperative isoflurane inhalation MAC and nicardipine, esmolol intervention were less, implying that in the G group in order to maintain hemodynamic stability and control the intensity of stress response, anesthesia of deeper depth and administration of vasoactive drugs were used, which was unfavorable for the postoperative awakening of anesthesia and hemodynamic stability.

Although this study employed local anesthetics of low-concentration and low-dose for epidural preemptive analgesia, a certain degree of blood pressure, heart rate decrease were observed, especially after the induction of anesthesia and before surgery. During this period this effect acted synergistically with the general anesthesia-inducing drugs without surgery stimulation. Actually it was due to the too weak stress response and more atropine and phenylephrine should be used to correct the hemodynamic disturbances. This study used phenylephrine for it had little effects on heart rate.

Before pneumoperitoneum, surgical stimulation was small and anesthesia was relatively deep. But for most patients the depth of anesthesia could be controlled and occasionally blood pressure and heart rate needed to be increased, especially in the GE group (**Table 2**). After the establishment of pneumoperitoneum, the situation was just the opposite. During the extubation with light anesthesia, blood pressure and heart rate needed to be lowered. There were more cases in the G group and probably no significant difference existed. This could be attributed to no intraoperative additional epidural drug administration, anesthesia subsidence and intolerance of the endotracheal tube. The stress caused by the operative pain and pneumoperitoneum accounted for a small portion. In this study, all patients safely went through the perioperative period without the complications related to anesthesia, indicating that epidural preemptive analgesia for laparoscopic adrenalectomy could reduce the intraoperative stress intensity. The anesthesia was more stable and awakening was smooth and safe. However, it should be paid attention to the anesthesia management after the anesthesia and before the surgery. It was also necessary to adequately expand the volume and use vasoactive drugs to correct the possible hemodynamic disturbances. In addition, for patients with active tumor endocrinal activity and difficulty in preoperative blood pressure control, the effects and safety of this method need further study.

Disclosure of conflict of interest

None.

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