Combined acupuncture and general anesthesia on immune and cognitive function in elderly patients following subtotal gastrectomy for gastric cancer

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Abstract. This study investigated the effects of acupuncture combined with general anesthesia on postoperative immune and cognitive functions in elderly patients undergoing subtotal gastrectomy. We recruited 96 elderly patients who received anesthesia for subtotal gastrectomy and randomly divided them into control (n=48) and experimental (n=48) groups. The control group received general anesthesia and the experimental group received combined acupuncture and general anesthesia. We measured hemodynamic immediately before and after anesthesia induction, and immune observations before and after surgery. We found no significant differences in mean heart rate (HR), mean oxygen saturation (SpO2), and partial pressure of end-tidal carbon dioxide (PETCO2) in the perioperative period between the two groups. Mean arterial pressure (MAP) was lower in the experimental group than that in the control group (P<0.05). The levels of cluster of differentiation 3 (CD3+), CD4+ and CD4+/CD8+ in both groups were significantly lower after surgery in both groups (P<0.05). We also found some time-points in which the immune markers where significantly higher in the experimental group. In terms of adverse reactions, there were no differences in nausea, vomiting, and hypoxemia between the two groups (P>0.05), but the incidence of delayed recovery and postoperative agitation were significantly lower in the experimental group compared with those in the control group (P<0.05). One day after surgery, the experimental group showed better protection of cognitive function than the control group (P<0.05). Overall, combined acupuncture and general anesthesia in elderly gastric cancer patients receiving subtotal gastrectomy showed more stable hemodynamics and fewer stress responses during surgery. Thus, combined acupuncture and general anesthesia can shorten the recovery time from anesthesia, have less negative effects on immune function and decrease the incidence of postoperative cognitive impairment.

Introduction

The continuous ageing of the population and the change in eating habits, the number of elderly patients with gastric cancer has risen together with the overall increase in disease incidence. At present, the incidence and death rate of gastric cancer are second among tumors (1). Affected by imbalanced access to medical care and low awareness of the presentation of gastric cancer among other factors, gastric cancer is typically diagnosed in advanced stages. In medium and advanced stages, most tumors infiltrate into the submucosa and muscularis, or reached the serosa across the muscularis (2,3). Therefore, the only option at this time is subtotal gastrectomy. With the rapid development of laparoscopic techniques, laparoscopy-assisted proximal subtotal gastrectomy has been widely applied in clinical practice, which enables thorough lymph node dissection (4). Immune dysfunction easily occurs because of surgery trauma, stress due to anesthesia, and compromised autoimmunity in elderly gastric cancer patients (5). Post-operative cognitive dysfunction (POCD) is one of the most distressing surgical problems (6). Acupuncture analgesia has a long history in China, and the combined acupuncture/general anesthesia has a good regulatory effect that is hard to be substituted by drugs. Here, we analyzed the immune and cognitive functions after general anesthesia in elderly patients undergoing subtotal gastrectomy, providing the basis for fast recovery and the prevention of POCD post-surgery.

Materials and methods

General subject information. We recruited 96 elderly patients that received general anesthesia for subtotal gastrectomy from January to December, 2016. Inclusion criteria: i) diagnosed with gastric cancer via electronic gastroscope biopsy, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI); ii) received surgical treatments and had complete medical records; iii) signed informed consent. Exclusion criteria: i) tumors with a maximum diameter >10 cm;

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Table I. General information sheet of research subjects.

Item	Control group (n=48)	Experimental group (n=48)	t/χ^2	P-value
Sex (male/female)	30/18	28/20	0.044	0.835
Age (years)	60-80	60-85		
Average age (years)	68.36±5.43	68.74±5.57	0.338	0.736
Adenocarcinoma differentiation (n, %)				
Well-differentiated	23 (47.92)	21 (43.75)	0.171	0.918
Moderately differentiated	15 (31.25)	16 (33.33)		
Poorly differentiated	10 (20.83)	11 (22.92)		
Tumor size (n, %)				
<3 cm	14 (29.17)	12 (25.0)	0.222	0. 895
3-5 cm	24 (50.0)	25 (52.08)		
>5 cm	10 (20.83)	11 (22.92)		

ii) distant metastases; iii) other malignant tumors. Patients were randomly divided into experimental (n=48) and control (n=48) groups by a random number table. The differences in patient data between the two groups were not statistically significant (P>0.05) (Table I).

Anesthesia. Patients fasted for 6 h before surgery. 0.1 g phenobarbital sodium (Tianjin Kingyork Group, approval no. NMPN H12020381) and 0.5 mg atropine (Jiangsu Lianshui Pharmaceutical, approval no. NMPN H32020166) were injected intramuscularly 30 min before the anesthesia, and arterial blood gas and blood pressure were monitored.

Only general anesthesia was used in the control group. After mask oxygen inhalation, midazolam (Yichang Humanwell Pharmaceutical, approval no. NMPN H20067040) at a dose of 0.05 mg/kg, fentanyl (Yichang Humanwell Pharmaceutical, approval no. NMPN H42022076) at a dose of 4 μg/kg, vecuronium bromide (Jiangsu Nhwa Pharmaceutical, approval no. NMPN H20113296) at a dose of 0.12 mg/kg, and propofol (Xi'an Libang Pharmaceutical, approval no. NMPN H20010368) at a dose of 2.5 mg/kg were injected intravenously. Trachea intubation was executed after the muscles were relaxed, and then it was connected to an all-round anesthetic machine (Drager, Lübeck, Germany) for intermittent positive pressure ventilation: tidal volume, 8-10 m/kg; respiratory rate, 12 breaths/min: partial pressure of end-tidal carbon dioxide (PETCO2), 30-40 mmHg. Intermittent bolus injection of 2 μg/kg/h fentanyl and 4 mg/kg/h propofol were performed and 0.1 mg/kg/h vecuronium bromide was pumped into vein to maintain the anesthesia.

Combined acupuncture and general anesthesia was used in the experimental group. Acupoints Zusanli (ST 36), Neiguan (PC 6), Hegu (LI 4), and Shangjuxu (ST 37) were positioned on both sides, and acupunctured after routine disinfection. After needling sensation was achieved, the filiform needles were connected with the electronesthesia apparatus at 80-90 times/min frequency. Then, the intensity was gradually increased to the level that was bearable to the patients and the stimulation time was 15-20 min. After that, the same methods applied in the control group were used for induction of general anesthesia.

Surgery. The patients were in supine position with legs wide apart. An observation hole was set around the umbilicus in which a cavity mirror was placed. Three to four surgical holes were selected to place the laparoscope. Lymph nodes in the pyloric region, upper region of pancreas, lesser curvature of stomach, hilus of spleen, and left cardiac region were dissected in sequence. A median incision was made lengthwise under the xiphoid and then the body of the stomach was taken out of the abdominal cavity after a protector was put in the incision. The proximal portion of the stomach was resected and a no. 24 stapler was implanted for stoma of remnant stomach under the laparoscope; the abdominal cavity was washed to place the drainage tube after the anterior wall of the stomach was sutured.

Immune indexes. Venous blood (5 ml) of the patients were collected 30 min before anesthesia (C0), during surgery (C1), immediately after surgery (C2), 24 h after surgery (C3), and 72 h after surgery (C4). Then, the venous blood was separated by centrifugation and serum was extracted. Anti-human cluster of differentiation 3 (CD3), CD4, and CD8 antibodies were added separately into the serum and incubated in the dark at 4°C for 30 min. The percentages of CD3+, CD4+ and CD8+ were measured using flow cytometry (Partec, Münster, Germany).

Evaluation methods. For hemodynamics, we measured heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO2), and PETCO2 immediately before anesthesia induction (T1), 1 min after intubation (T2), 5 min into the surgery (T3), and 10 min into the surgery (T4).

Venous blood was collected at C0, C1, C2, C3 and C4, and the levels of T-lymphocyte subsets (CD3+, CD4+, CD8+ and CD4+/CD8+) were measured using flow cytometry. Adverse reactions, including nausea and vomiting, hypoxemia, delayed recovery, and postoperative agitation, we recorded.

The Montreal Cognitive Assessment (MoCA) scale (7) and Mini-Mental State Examination (MMSE) (8) were used to evaluate the cognitive function one day before and one day after surgery. The MoCA scale was evaluated in 8 aspects: space and executive capability, memory, attention, naming, language,

Table II. Hemodynamic indexes in different periods.

Index	Group	Cases	T1	T2	T3	T4
HR (bpm)	Experimental	48	85.13±6.35	74.73±6.42[a]	68.24±5.35[a]	64.74±5.78[a]
	Control	48	84.38±6.72	75.05±6.13[a]	67.94±5.38[a]	65.13±5.48[a]
SpO2 (mmHg)	Experimental	48	99.36±0.41	98.74±0.35	97.56±0.28	99.48±0.27
	Control	48	99.23±0.32	98.58±0.28	97.42±0.37	99.36±0.18
PETCO2 (mmHg)	Experimental	48	35.74±1.46	35.44±1.36	35.58±1.27	35.93±1.33
	Control	48	35.83±1.32	35.56±1.72	35.74±1.35	35.78±1.57

[a]P<0.05 compared with T1 within the group. HR, heart rate; PETCO2, partial pressure of end-tidal carbon dioxide; SpO2, oxygen saturation.

Table III. MAP levels in different periods (mmHg).

Group	Cases	T1	T2	T3	T4
Experimental	48	56.83±3.72	67.38±4.26	65.32±3.25	57.14±3.45
Control	48	58.15±3.65	79.56±4.38	75.63±3.47	59.48±3.63
t-test		1.755	13.811	15.024	3.237
P-value		0.083	<0.001	<0.001	0.002

MAP, mean arterial pressure.

Table IV. CD3+ levels at different times (%).

Group	C0	C1	C2	C3	C4
Experimental	54.83±3.54	50.35±3.42	43.57±3.45[a]	44.64±3.66[a]	47.54±3.63[a]
Control	55.16±3.35	51.48±3.57	45.46±3.37[a]	49.57±3.73[a]	49.18±3.78[a]
t-test	0.469	1.584	2.715	6.536	2.168
P-value	0.640	0.117	0.008	<0.001	0.033

[a]P<0.05 compared with C0 within the group.

delayed recall, abstract thinking and orientation, with a total of 30 points. Score <26 indicated impairment of cognitive functions. MMSE was graded in 5 aspects: orientation, language, recall, attention, and calculating ability. i) Mild cognitive impairment: 21-24 points; ii) moderate cognitive impairment: 11-20 points; iii) severe cognitive impairment: 0-10 points.

Statistical analysis. SPSS 19.0 (SPSS, Chicago, IL, USA) software was used for data processing. All the measurement data were presented as mean ± standard deviation (mean ± SD). t-test was used for comparing intra-group data at different time-points; enumeration data were presented as rates and χ^2 test was applied. P<0.05 suggested that the difference was statistically significant.

Results

Hemodynamics. We first compared the hemodynamic indexes of the patients during different phases of anesthesia (Table II).

HR significantly decreased in T3 compared with T1 in both groups, but we found no significant differences between the two groups in HR, SpO2 (no hypoxemia occurred during the operation), and PETCO2 (<40 mmHg in both groups). However, MAP after anesthesia was significantly lower in the experimental group than that in the control group (Table III).

Immune indexes. The levels of CD3+, CD4+, and CD4+/CD8+ were significantly lower in both groups at C2-C4 compared with those at C0 (Tables IV, V and VII). At C2, the level of CD3+ was significantly higher in the experimental group than that in the control group (Table IV). At C3, the levels of CD3+ and CD4+ were higher in the experimental group than those in the control group (Tables IV and V). At C4, the levels of CD3+, CD4+ and CD4+/CD8+ were significantly higher in the experimental group than those in the control group (Tables IV-VII).

Adverse events. The analysis of adverse reactions after operation showed no obvious differences in nausea and vomiting,

Table V. CD4$^+$ levels at different times (%).

Group	C0	C1	C2	C3	C4
Experimental	32.76±3.72	28.76±3.14	23.46±3.38[a]	21.18±3.83[a]	23.48±3.15[a]
Control	33.01±3.34	28.36±3.16	23.62±3.45[a]	25.65±3.15[a]	25.25±3.42[a]
t-test	0.346	0.622	0.230	6.254	2.637
P-value	0.730	0.535	0.819	<0.001	0.010

[a]P<0.05 intra-group comparisons.

Table VI. CD8$^+$ levels at different times (%).

Group	C0	C1	C2	C3	C4
Experimental	21.74±3.06	20.82±3.25	20.45±3.15	22.86±3.13	23.52±3.27
Control	21.92±3.12	21.06±3.34	20.73±3.17	23.23±3.28	23.48±3.38
t-test	0.285	0.357	0.434	0.565	0.059
P-value	0.776	0.722	0.665	0.573	0.953

P<0.05 compared with C0 within the group.

Table VII. CD4$^+$/CD8$^+$ levels at different times (%).

Group	C0	C1	C2	C3	C4
Experimental	1.54±0.46	1.21±0.34	1.17±0.37[a]	1.01±0.24[a]	1.03±0.34[a]
Control	1.53±0.42	1.27±0.47	1.19±0.35[a]	1.05±0.32[a]	1.29±0.38[a]
t-test	0.111	0.717	0.408	0.693	3.533
P-value	0.912	0.475	0.684	0.490	0.001

[a]P<0.05 compared with C0 within the group.

Table VIII. Adverse reactions after operation in two groups (n, %).

Group	Cases	Nausea and vomiting	Hypoxemia	Postoperative agitation	Delayed recovery
Experimental	48	3 (6.25)	1 (2.08)	0 (0.00)	2 (4.17)
Control	48	4 (8.33)	2 (4.17)	7 (14.58)	3 (6.25)
χ^2 test		0.001	0.002	5.547	0.001
P-value		0.999	0.982	0.019	0.999

Table IX. MoCA and MMSE scores in two groups.

Group	MoCA (points)				MMSE (points)			
	1 day before operation	1 day after operation	t-test	P-value	1 day before operation	1 day after operation	t-test	P-value
Experimental	28.63±1.54	26.84±1.82	5.202	<0.001	30.38±1.56	26.48±1.46	12.646	<0.001
Control	28.72±1.62	25.37±1.75	9.733	<0.001	29.94±1.62	23.53±1.58	19.625	<0.001
t-test	0.279	4.034			1.355	9.500		
P-value	0.781	0.001			0.179	<0.001		

MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination.

hypoxemia, and delayed recovery between the two groups. However, the incidence of postoperative agitation was significantly decreased in the experimental group (0 cases) compared with that in the control group (7 cases) (Table VIII).

Cognitive function. The MoCA and MMSE scores after operation were lower compared with those before operation in both groups. The decline in the experimental group was less pronounced than that in the control group (Table IX).

Discussion

Water pollution, overwork, unhealthy diet (excessive salt intake, fried, smoked and pickled food, hot diets and moldy food) as well as genetic and immune factors are implicated in gastric cancer (9). In the advanced stage, the tumors can invade the mucosa and submucosa, muscularis as well as serosa (10), which is often treated with surgery. Between total gastrectomy and proximal subtotal gastrectomy, the latter has the following advantages: Adequate excision of tumors, complete dissection of lymph nodes, simple resection and anastomosis as well as retainable gastric functions. Therefore, it is generally well accepted by patients, particularly elderly patients (11).

In the perioperative period for subtotal gastrectomy, both the surgery and anesthesia can cause stress leading to increased HR, elevated blood pressure and other changes (12). We show that the two anesthesia methods studied here caused no differences in SpO2, PETCO2 and HR. However, MAP after anesthesia was lower in experimental group, suggesting that adding acupuncture reduced hypertension responses during surgery and regulate the blood pressure in the recovery period, instead of causing abnormal changes in hemodynamics.

Generally, elderly patients have weak immunity and the stress caused by surgery can further suppress immunity (13). CD3$^+$ represents all the T lymphocytes in the body. CD4$^+$ belongs to the inducer T cell subsets, which have positive regulation of immunity. CD8$^+$ belongs to the suppressor T cell subsets, which can cause disorders of immune functions (14). We found that the levels of CD3$^+$, CD4$^+$ and CD4$^+$/CD8$^+$ were lower after surgery in both groups. However, we found partial evidence for stronger immunity in the experimental group: C3$^+$, C4$^+$ and CD4$^+$/CD8$^+$ were higher in the experimental group at some time-points. The stress responses caused by general anesthesia can increase the secretion of catechol and epinephrine, thus leading to suppression of immune functions of the T lymphocytes (13). However, combined acupuncture and general anesthesia can control the stress responses and partially protect immune function. Systematic and bidirectional regulation on multiple organs can be realized via electro-acupuncture stimulation, which can not only mobilize pain suppression but also suppress physiological disorders and reduce stress responses to inhibit the inflammatory responses and maintain stable circulation (15,16).

POCD is a mild neurocognitive dysfunction that is reversible. It often occurs after major surgeries. In particular, patients can develop cognitive impairment and mental retardation in respect to social skills, memory, and orientation after anesthesia. These problems are specifically manifested as anxiety, personality change, memory loss, abnormal cognitive

ability, and disorders of mental system (17). Evidence-based medicine studies have shown that general anesthesia can lead to morphologic and biological changes of neurons, thus causing apoptosis and cell loss. Elderly patients are especially vulnerable to the effects of general anesthesia and the incidence of POCD is higher among them (18). This study showed no obvious differences in nausea, vomiting, and hypoxemia between the two groups. But the incidence of postoperative agitation was decreased in the experimental group compared with that in the control group. One day after surgery the MoCA and MMSE scores were better in the experimental group than those in the control group due to the reduction in the number of synapses and a decrease in synaptic density in the brain caused by general anesthetics. Our results show that POCD is a highly prevalent complication of major surgery (18). Combined acupuncture and general anesthesia has unique features that prevents noxious stimulation by analgesia. Acupuncture anesthesia is a non-pharmacological form of anesthesia by pain modulation mechanism activated by acupoint stimulation. On achieving the same anesthetic effect, acupuncture anesthesia can considerably reduce the use of anesthetic drugs, lowering the incidence of adverse reactions. Furthermore, acupuncture combined with drugs can effectively suppress the central nervous system, improve microcirculation and oxygen metabolism of brain tissues, increase cerebral blood supply, relieve cerebral edema, and reduce inflammatory responses in the hippocampus caused by inflammatory factors crossing the blood-brain barrier (19). In addition, acupuncture anesthesia can reduce the accumulation of Ca^{2+} in brain neurons, prevent Ca^{2+} overload, mitigate or avoid necrosis of the neurons, and have a protective effect on the ischemic injury of neurons. As a result, the occurrence of cognitive impairment is decreased (20).

In conclusion, compared with simple general anesthesia, combined acupuncture and general anesthesia can stabilize the hemodynamic indexes in elderly patients undergoing subtotal gastrectomy, reduce adverse reactions after operation, and effectively improve immune function. Therefore, this practice should be further popularized.

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