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Original Article

Effects of electroacupuncture at Baihui and Dazhui on perioperative neurocognitive impairment and S100-β, LC3-II, Beclin-1 in patients with colon cancer

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Abstract: Objective: To investigate the effects of electroacupuncture pre-stimulation on perioperative neurocognitive disorders (PNDs) in patients undergoing colon cancer surgery. Methods: A total of 80 elderly patients with colon cancer undergoing elective surgery were selected as subjects. Patients in an observation group (N=40) were given electroacupuncture pre-stimulation at Baihui and Dazhui points, while those in a control group (N=40) were given sham electroacupuncture pre-stimulation. The Mini-Mental State Examination (MMSE), self-rating anxiety scale (SAS), Activity of Daily Living Scale (ADL), as well as the levels of microtubule-associated protein light chain 3II (LC3-II), Bcl-2 homologous domain protein antibody 1 (Beclin-1) and central nerve specific protein S100β before and after treatment were compared. Results: Compared with those before treatment, no significant differences were found in the scores of MMSE, SAS and ADL at 7 d after treatment in both groups, while MMSE scores were significantly lower and the scores of SAS and ADL were obviously more at 1 d and 3 d after treatment in both groups. Moreover, at 1 d and 3 d after treatment, the MMSE score in the observation group was significantly higher than that in the control group, while the scores of SAS and ADL in the observation group were lower than those in the control group (all $P<0.05$). Compared with those after treatment in the control group, the level of S100β was significantly decreased, while the levels of LC3-II and Beclin-1 were obviously increased in the observation group (all $P<0.05$). Conclusion: Electroacupuncture pre-stimulation at Baihui and Dazhui points could effectively reduce neurological damage and prevent PNDs in patients undergoing colon cancer surgery through improving the cognitive functions, anxiety states and self-care ability. The observed changes in levels of S100β, LC3-II and Beclin-1 may be associated with the beneficial effects of electroacupuncture pre-stimulation on PNDs in these patients.

Keywords: Colon cancer, perioperative neurocognitive impairment, electroacupuncture, therapeutic effect

Introduction

Colon cancer is a significant contributor to cancer-related mortality. In recent years, due to changes in diet, environmental exposure, lifestyle factors and advancements in cancer screening technology, the incidence of early-onset colon cancer has shown a rapid upward trend [1, 2]. Surgical treatment is the first choice for early-onset colon cancer, but there is still a certain risk of complications during the perioperative period, which may not only affect the surgical outcomes and postoperative rehabilitation effects, but also has a negative impact on the prognosis of patients. Among them, perioperative neurocognitive disorders (PNDs) are common complications in anesthesia surgery. As surgical anesthesia becomes more prevalent and medical technologies continue to advance, PNDs have gained increasing attentions [3]. PNDs include postoperative delirium, delayed recovery of neurological function, mild or severe cognitive impairment according to the time of occurrence during the perioperative period [4]. Postoperative delirium is closely related to long-term cognitive function, and may even increase the incidence of Alzheimer's disease [5]. It was reported that the risk of postoperative delirium in elderly patients with colon cancer undergoing surgical treatment was relatively high [6]. The occurrence of PNDs can result in prolonged hospitalization time for patients, leading to increased social and economic burden on patients and their families [7]. Therefore, it is necessary to improve the level of prevention and management of PNDs in patients undergoing colon cancer surgery.

The pathogenesis of PNDs is relatively complex and not fully understood. It is believed that the pathogenesis is closely related to inflammatory reactions, oxidative stress and cell apoptosis, and autophagy is considered to be one of the key mechanisms involved in the occurrence and development of PNDs. Autophagy is a cellular process that involves lysosomal degradation of damaged organelles and macromolecular substances within cells. It plays a critical role in various pathophysiological mechanisms, including the regulation of cell growth and metabolism, the digestion and degradation of intracellular aging organelles and abnormal proteins such as Aβ and maintenance of cellular environmental homeostasis. Microtubule-associated protein light chain 3II (LC3-II) and Bcl-2 homologous domain protein antibody 1 (Beclin-1) have been widely considered to be markers of autophagy. It was reported that LC3-II and beclin-1 levels were directly correlated with autophagic activity [8]. Some studies showed that autophagy dysfunction was involved in many neurodegenerative diseases including PNDs [9]. Another study revealed that impaired autophagic activity in the hippocampus was associated with cognitive impairment in diabetic rats [10]. It has been reported that upregulation of autophagy plays a crucial neuroprotective role in neurodegenerative disorders and brain injury [11]. Therefore, it was considered that there may be a link between autophagy and PNDs.

In recent years, traditional Chinese medicine treatment has been widely applied for the prevention of PNDs, and its efficacy has been clinically recognized [12]. Acupuncture and moxibustion are important therapeutic methods in traditional Chinese medicine and have been used for centuries to treat various health conditions, including cognitive functional diseases [13]. The electroacupuncture pre-stimulation combines the benefits of traditional acupuncture and moxibustion treatment, while also incorporating the physiological effects of electric stimulation. Previous studies have shown that the electroacupuncture pre-stimulation had a definite effect on neurocognitive impairment [14]. However, the majority of studies investigating the effects of electroacupuncture pre-stimulation on PNDs were conducted in animal models, and the exact mechanisms are not yet clear. In order to further explore the clinical effects of electroacupuncture pre-stimulation in the treatment of PNDs, 80 elderly patients with colon cancer admitted to The First People's Hospital of Wenling from January 2021 and January 2023 were selected as the research subjects in this study. Through analyses, the clinical efficacy between electroacupuncture pre-stimulation and sham electroacupuncture were compared, and the possible mechanisms were investigated. The findings of this study could potentially offer valuable clinical insights for the management of PNDs in patients undergoing colon cancer surgery.

Material and methods

General information

This is a retrospective study. From January 2021 and January 2023, 80 elderly patients undergoing colon cancer surgery in Department of Anesthesiology, The First People's Hospital of Wenling were selected as study subjects. According to the treatment methods, these patients were divided into an observation group and a control group, with 40 cases in each group. The patients in the observation group underwent electroacupuncture, while those in the control group received sham electroacupuncture. The Ethics Committee of The First People's Hospital of Wenling approved this research (No. KY-2023-1009-01).

Inclusion criteria: (1) Patients met the diagnostic criteria of colon cancer and had surgical indications of colon cancer [15]. (2) Patients were 65 to 89 years old. (3) Patients received elective surgery for colon cancer under general anesthesia and met the American Association of Anesthesiologists (ASA) II-III classification criteria. (4) Patients had no neurocognitive impairment before surgery, with good mental state and a Mini-Mental State Examination (MMSE) score of more than 23 points after the revision of education level. (5) Patients signed an informed consent. (6) Patients had complete medical records.

Exclusion criteria: (1) Patients had central nervous system diseases or psychological disease. (2) Patients were not able to communicate due to serious vision or hearing impairment or other reasons. (3) Patients had a history of long-term alcoholism or current use of sedatives and antidepressants. (4) Patients dropped out of the treatment due to strong resistance, changes in illness, serious adverse reactions or other reasons.

Data collection

General data of eligible patients, including sex, age, average education years, body mass index (BMI), ASA II/III, and time of operation were collected from the patient records.

The evaluated data, which comprised cognitive function, anxiety state, self-care ability, the levels of autophagic protein and specific protein of central nervous system, were also extracted. We performed a manual review and verification of the printed medical records to ensure the accuracy of the collected data.

Treatment methods

Electroacupuncture pre-stimulation before surgery: In the observation group, patients were given electroacupuncture pre-stimulation at Baihui and Dazhui using 40 mm acupuncture and moxibustion needles. After Qi was obtained, G6805-2 type electroacupuncture instrument which was purchased from Shanghai Huayi Medical Instrument Co., Ltd. was connected, with a frequency of 2-15 Hz. The needles were kept in place for 30 min, one time a day. The electroacupuncture stimulation was performed at the same hour every day. The electroacupuncture pre-stimulation was conducted for 5 days prior to the day of surgery.

In the control group, the patients received sham electroacupuncture pre-stimulation. The acupoints was selected to be one inch away from Baihui and Dazhui points. After the insertion, the special electroacupuncture instrument was connected, but the middle wire was disconnected without affecting the normal appearance. The frequency and retention time of the needles were the same as those in the observation group. Although the instrument appeared to be connected, actually it was not powered on, despite showing a connected status.

Anesthesia during the perioperative period: The patients in both groups received the same anesthesia strategy during the perioperative period. A rapid anesthesia induction was performed with intravenous injection of 1-2 mg/kg propofol, 0.4 μg/kg sufentanil and 0.6 mg/kg rocuronium, then the tracheal intubation was conducted. During the operation, 4-6 mg/kg·h propofol and 0.1-0.3 μg/kg·h remifentanil were used for anesthesia maintenance, and rocuronium was injected intermittently to maintain muscle relaxation. The bispectral index on the electroencephalogram was kept between 40 and 60, and the end-expiratory carbon dioxide concentration was kept between 35 mmHg and 45 mmHg. Patients from both groups were given the same type and dose of drugs for patient-controlled intravenous analgesia after surgery.

Observation indices

In this research the primary outcome measure was cognitive function. The secondary indexes included anxiety state, self-care ability, the levels of autophagic protein and specific proteins of the central nervous system.

The cognitive function was evaluated using MMSE [16] before surgery and at 1 d, 3 d and 7 d after the surgery. The scale of MMSE included five dimensions; orientation, memory, attention and concentration, language ability, and visuospatial ability. The total score was 30 points. A higher score indicated better cognitive function.

The anxiety state was evaluated in patients using self-rating anxiety scale (SAS) [17] before the surgery and at 1 d, 3 d and 7 d after the surgery. The SAS scale includes 20 items, which were calculated using the four-grade scoring method and converted into centesimal scores. A higher score indicated more serious anxiety.

The self-care ability was evaluated in patients using the activity of daily living scale (ADL) [18] before the surgery and at 1 d, 3 d and 7 d after the surgery. ADL was used to evaluate two aspects, physical self-care ability (6 items such as going to the bathroom, eating and dressing)

Table 1. The comparison of general information between the observation group and the control group

Parameters		Observation group (N=40)	Control Group (N=40)	t/χ² value	*P* value
Sex	Male	22	20	0.731	0.322
	Female	18	20		
Age (years)		73.3±10.2	73.5±10.0	0.804	0.419
Average education years		8.9±2.4	8.8±2.5	0.511	0.517
BMI (kg/m²)		24.9±1.6	25.0±1.5	0.491	0.548
ASA II/III (cases)		10/33	12/28	0.672	0.445
Time of operation (h)		3.5±0.5	3.7±0.6	0.568	0.439
Hypertension (n)		8	10	0.684	0.417
Diabetes (n)		9	6	0.702	0.368
Estimated blood loss (mL)		124.5±11.6	130.7±12.2	0.775	0.452

Note: BMI: Body mass index. ASA: American Society of Anesthesiologists.

Table 2. Comparison of cognitive function between the observation group and the control group

Groups	Before surgery	At 1 d after surgery	At 3 d after surgery	At 7 d after surgery
Observation group (N=40)	25.67±2.41	23.13±2.11*	24.53±2.34*	25.38±2.67
Control group (N=40)	25.39±2.37	21.57±2.03*	22.49±2.18*	25.51±2.06
t value	0.524	3.370	4.034	0.244
P value	0.602	0.001	<0.001	0.808

Note: Compared with before surgery in the same group, *P<0.05.

and instrumental self-care ability (8 items such as making phone calls, shopping and doing housework). There were a total of 14 items in this scale. A four-level scoring method was used, with a total score ranging from 14 to 56 points. A higher score indicated lower self-care ability.

The levels of autophagic protein and specific proteins of the central nervous system were compared between two groups before and after the surgery. In both groups, 4 ml of fasting venous blood was collected and centrifuged (3000 r/min, 10 min). The enzyme-linked immunosorbent assay kits, which were purchased from Wuhan Hualianke Biotechnology Co., Ltd., were used to measure the levels of S100 β (CSB-E08065h), microtubule-associated protein light chain 3II (LC3-II) (CSB-E09040h) and Bcl-2 homologous domain protein antibody 1 (Beclin-1) (CSB-E08075h).

Statistical methods

All the clinical data collected in this study were analyzed using SPSS version 23.0. The measurement data were expressed as Mean ± Standard deviation. For intragroup before-after comparison, paired sample t test was performed. For between-group comparison, independent sample t test was conducted. For the comparison among multi-time data, repeated measures ANOVA followed by post hoc Bonferroni test was performed. The comparison among more than three groups was performed using one-way ANOVA followed by Bonferroni post hoc tests. The count data were presented as percentages/cases. The comparison among groups was performed using χ^2 test. $P<0.05$ indicated statistically significant differences.

Results

Comparison of general information

There was no significant difference in the sex, age, average education years, BMI, ASA II/III and time of operation between the observation group and the control group (all $P>0.05$). Therefore, the two groups were comparable. See **Table 1**.

Comparison of cognitive function between the two groups

As described in **Table 2**, there were significant differences in MMSE score among groups

Table 3. Comparison of SAS scores between the two groups

Groups	Before surgery	At 1 d after surgery	At 3 d after surgery	At 7 d after surgery
Observation group (N=40)	54.13±4.29	57.46±4.75*	55.26±3.69*	52.17±3.58
Control group (N=40)	54.34±4.22	59.83±4.96*	57.45±3.22*	52.46±3.24
t value	0.221	2.183	2.828	0.380
P value	0.826	0.032	0.006	0.705

Note: Compared with before surgery in the same group, *P<0.05.

Table 4. Comparison of activity of daily living scale between the two groups

Groups	Before surgery	At 1 d after surgery	At 3 d after surgery	At 7 d after surgery
Observation group (N=40)	15.49±2.57	19.44±2.45*	17.13±2.31*	15.22±2.67
Control group (N=40)	15.32±2.61	21.32±2.59*	19.48±2.49*	15.18±2.32
t value	0.294	3.335	4.376	0.072
P value	0.770	0.001	<0.001	0.943

Note: Compared with before surgery in the same group, *P<0.05.

before surgery, at 1 d after surgery and 3 d after surgery in both groups. No significant differences were found in MMSE score at 7 d after surgery in both groups when comparing with that before treatment. The MMSE scores at 1 d and 3 d after surgery in both groups were significantly reduced in contrast to that before treatment, and there were significant differences. There were not significant differences in MMSE score before treatment and at 7 d after treatment between the observation group and the control group. Compared with those in the control group, the MMSE scores in the observation group were significantly increased at 1 d (23.13±2.11 vs. 21.57±2.03, P=0.001) and 3 d (24.53±2.34 vs. 22.49±2.18, P<0.001) after surgery, and statistical differences were found.

Comparison of SAS scores between the two groups

As shown in **Table 3**, there were significant differences in SAS score among groups before surgery, at 1 d after surgery and 3 d after surgery in both groups. Compared with that before surgery, no statistical difference was observed in SAS scores at 7 d after surgery in both groups. SAS scores at 1 d and 3 d after surgery in both groups were significantly increased in contrast to that before surgery, and significant differences were found. There was no difference in SAS scores before surgery and at 7 d after surgery between the observation group and the control group. Compared with those in the control group, the SAS scores in the observation group were obviously decreased at 1 d (57.46±4.75 vs. 59.83±4.96, P=0.032) and 3 d (55.26±3.69 vs. 57.45±3.22, P=0.006) after surgery, and statistically significant differences were observed.

Comparison of ADL scores between the two groups

As shown in **Table 4**, there were significant differences in SAS scores among groups before surgery, at 1 d after surgery and 3 d after surgery in both groups. Compared with that before surgery, no obvious difference was found in ADL scores at 7 d after surgery in both groups. Compared with those before surgery, ADL scores at 1 d and 3 d after surgery were markedly increased in both groups, and the statistical differences were observed (all P<0.05). There was no significant difference in ADL scores before surgery and at 7 d after surgery between the observation group and the control group. Compared with those in the control group, the ADL scores in the observation group were markedly reduced at 1 d (19.44±2.45 vs. 21.32±2.59, P=0.001) and 3 d (17.13±2.31 vs. 19.48±2.49, P<0.001) after surgery, and statistically significant differences were found.

Comparison of autophagic proteins and specific proteins of the central nervous system between the two groups

Before surgery, there was no significant differences in levels of S100-β, LC3-II, Beclin-1 between the two groups. Compared with those before surgery, the levels of S100-β,

Table 5. Comparison of S100-β, LC3-II and Beclin-1 levels between the two groups

Groups	S100-β (ng/L)		LC3-II (ng/ml)		Beclin-1 (ng/ml)	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
Observation group (N=40)	543.75±78.03	673.36±95.68*	2.43±0.25	3.25±0.39*	2.45±0.16	3.04±0.47*
Control group (N=40)	550.43±78.91	946.65±97.84*	2.44±0.22	2.78±0.25*	2.41±0.19	2.81±0.40*
t value	0.381	12.630	0.190	6.417	1.019	2.357
P value	0.705	<0.001	0.850	<0.001	0.312	0.021

Note: Compared with before surgery in the same group, *P<0.05.

LC3-II and Beclin-1 after surgery were significantly increased in both groups, and obvious differences were found (all P<0.05). Compared with those in the control group, the level of S100-β (673.36±95.68 vs. 946.65±97.84, P<0.001) in the observation group was significantly decreased after surgery, while the levels of LC3-II (3.25±0.39 vs. 2.78±0.25, P<0.001) and Beclin-1 (3.04±0.47 vs. 2.81±0.40, P= 0.021) in the observation group were obviously increased. The differences were statistically significant between the two groups, as shown in **Table 5**.

Discussion

PNDs are typically classified in Chinese medicine under categories such as "dementia", "forgetfulness" or "stupidity", based on their etiology, pathogenesis, clinical manifestations and treatment. Traditional Chinese medicine considers that the brain is the sea of marrow, and the kidney dominates the bone and produces marrow. However, elderly individuals may have weakened kidney essence, leading to inadequate nourishment of the brain marrow. Surgical anesthesia could result in the obstruction of Qi, blood stasis, blockage of meridians, loss of brain function, and loss of vital activity [19]. Its basic pathogenesis is the deficiency of the root (deficiency of the liver, kidney, qi and blood) and excessive superficial (stagnation of qi, blood stasis, and toxin). The treatment should address the underlying deficiency. This may include methods to eliminate the evil, supplement Qi, activate the blood circulation, and remove blood stasis and unblock collaterals. Acupuncture and moxibustion is a commonly used external treatment in Chinese medicine. The Chinese medicine rehabilitation therapy based on acupuncture and moxibustion has been widely accepted for the treatment of postoperative cognitive dysfunction. Some studies found that acupuncture and moxibustion can intervene with the pathological mechanism of PNDs through multiple targets such as regulating cholinergic, activating anti-inflammatory pathway of microglia, inhibiting oxidative stress, reducing neuronal damage and enhancing synaptic plasticity [20].

Electroacupuncture stimulation is based on the acupuncture strategy derived from acupuncture and moxibustion. Through acupuncture and micro electrical stimulation of specific points, it can reduce analgesia, promote meridian flow, improve local blood circulation, etc. Compared with conventional acupuncture, electroacupuncture stimulation can accurately control the amount of stimulation, and it does not disrupt the normal physiological functions of the human body. Meanwhile, it has a definite effect on regulating the nervous system. However, preoperative stimulation can modulate nerve excitability in advance and potentially mitigate the risk of cognitive dysfunction risk events. The acupoints "Baihui" and "Dazhui" selected in this study belong to the Du meridian acupoints. Baihui is the "three yang and five meetings", and Dazhui is the "meeting of all yang". The Du meridian is closely associated with the brain. Acupuncture at the above two acupoints can stimulate the meridians, dredge the meridians and collaterals, promote the circulation of qi and blood for the brain, resulting in improved flow in the brain meridians and supporting the optimal functioning of the "house of the original spirit", which is associated with cognitive health [21]. It has been reported that electroacupuncture stimulation could improve cognitive dysfunction in elderly rats after operation by enhancing autophagy mechanism (LC3/Beclin1 protein) [22]. The results of this study showed that there was no statistical differences in the scores of MMSE, SAS and ADL between groups before surgery and at 7 days after the surgery in both groups, while MMSE scores were significantly lower and the scores of SAS and ADL were obviously increased in the two groups at 1 d and 3 d after the surgery in contrast to those before treatment. The changes in the scores of MMSE, SAS and ADL in the observation group were more significant than those in the control group (all P<0.05). This indicated that electroacupuncture pre-stimulation at Baihui and Dazhui points can effectively reduce the risk of cognitive function, as well as improve self-care ability and negative emotions. Surgery is a traumatic procedure that can impact immune and inflammatory mechanisms in patients, potentially leading to damage of brain cells and subsequent cognitive dysfunction. Simultaneously, factors such as reduced cognitive function and surgical trauma can significantly decrease the self-care ability of patients and lead to an increase in negative emotions. Electroacupuncture pre-stimulation can accelerate blood flow, improve blood circulation throughout the body (including brain tissue), promote the awakening of nerve cells in an inhibited state, and facilitate their quick recovery of excitability after operation. Also, it has potential benefits in reducing inflammation, apoptosis and autophagy, which may help protect brain tissue damage and subsequently reduce the risk of cognitive dysfunction. The levels of S100β, LC3-II and Beclin-1 were significantly increased in the two groups after the surgery in contrast to those before the surgery. The central nerve specific protein S100β in the observation group was lower than that in the control group, while the levels of autophagic protein LC3-II and Beclin-1 were significantly higher than those in the control group (all P<0.05). It was shown that electroacupuncture pre-stimulation at Baihui and Dazhui points can effectively affect autophagy mechanism, protect nerve function and reduce nerve injury. S100β protein is a specific marker of neuronal damage, and its increased level indicated that the central nervous system function is damaged to a certain extent [23]. LC3-II is an autophagic body marker protein, which can combine with the complex on the autophagic vesicle membrane and participate in the transport process of microtubule-associated proteins to the vesicle membrane. Beclin-1 is a specific gene that participates in the formation mechanism of autophagic vesicles and type III PIK complex, and can also induce other autophagy-related proteins to aggregate on the phagocytic vesicles, forming a double-layer membrane to protect autophagy. Up-regulation of LC3-II and Beclin-1 levels can affect the physiological process of autophagy, reduce the aggregation of nociceptive cells and proteins, and prevent neuronal apoptosis [24]. It was reported that electroacupuncture at Shenting and Baihui could effectively regulate the level of Beclin-1 protein and protect the brain tissue of rats [25]. The central nervous system faces potential damage during anesthesia, and electroacupuncture pre-stimulation at Baihui and Dazhui points has a protective effect on brain tissue and help prevents nerve function damage by improving the level of S100β and affecting the autophagy mechanism regulated by LC3-II and Beclin-1.

The present study does have some limitations. This study focused on the changes in cognition-related protein expression to reveal the potential mechanisms of electroacupuncture pre-stimulation in patients with PNDs, but different brain regions might be involved in PNDs after surgery. Moreover, this research is a single-center study, with small sample size and no subgroups comparison, therefore, lacking of long-term results and follow-up results. In the future, a multicenter controlled long-term follow-up study with large sample size is required for further confirmation.

In conclusions, electroacupuncture pre-stimulation at Baihui and Dazhui points has an obvious protective effect in patients undergoing colon cancer surgery. It can effectively improve cognitive function, reduce anxiety, enhance self-care ability, and minimize neurological damage by regulating the autophagy mechanism. These findings suggest that electroacupuncture pre-stimulation may be a valuable clinical approach for preventing PNDs and warrants further clinical promotion.

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Disclosure of conflict of interest

None.

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