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Effect of Qihuang Decoction on Gastrointestinal Motility and Secretory Function after Gastrectomy

Hui Peng[1,2,3], Feisheng Wei [1,2,3], Wenshan Jing [1,3], Zhou Zheng [1,2,3], Fuhai Zhou [1,3], and Qingsheng Yu [1,2,3*]

[1]Department of General Surgery, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, Anhui 230031, China

[2]Anhui University of Chinese Medicine, Hefei, Anhui 230031, China

[3]Institute of Chinese Medicine Surgery, Anhui Academy of Chinese Medical Sciences, Hefei, Anhui 230031, China

***Corresponding author:**

Qingsheng Yu,
Department of General Surgery, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei 230031, Anhui, China; Institute of Chinese Medicine Surgery, Anhui Academy of Chinese Medicine, Hefei 230031, Anhui, China.
Tel: 86-13866141906;
E-mail: qsy6312@163.com; ph136382333@126.com

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Keywords:

Postoperative Gastric Cancer; Gastrointestinal Motility; Gastroenterography; Gastrointestinal Hormones, Complication; Chinese Herbal Medicine

1. Abstract

1.1. Background and study aim: The study aimed to explore the effect of Qihuang decoction on gastrointestinal motility and secretory function after gastrectomy.

1.2. Methods: A total of 260 gastric cancer patients were randomly divided into research group and control group. The recovery time of gastrointestinal motility, changes of gastrointestinal angiography, secretions of gastrointestinal hormone and incidence of complications after gastric cancer operation were evaluated in two groups.

1.3. Results: After 7 days of treatment, Qihuang decoction can significantly improve the recovery time of resuming peristaltic sound, anal exhaust time, recovery time of anal defecation and time of resume oral intake in patients with gastric cancer after operation (P<0.001). And the time of meglumine diatrizoate reaching ileocecal junction and rectum in Qihuang decoction group was significantly shorter than that in control group (P<0.05). Fourteen days after operation, motilin (MOT), gastrin (GAS) and cholecystokinin (CCK) that can promote gastrointestinal motor function were significantly increased in Qihuang decoction group (P<0.001). In stark contrast, the hormones that inhibit gastrointestinal motor function, such as gastrointestinal peptide (GIP), vasoactive intestinal peptide (VIP) and somatostatin (SS), were all decreased in Qihuang decoction group at 3, 7 and 14 days after operation (P<0.05). Moreover, the incidence of postoperative complications in the Qihuang decoction group was 12.88% and 43% in the control group (P<0.001).

1.4. Conclusion: The early treatment of Qihuang decoction in the operation of gastric cancer is beneficial to restore gastrointestinal motor function and reduce the incidence of complications, which might be releated to the secretion of certain gastrointestinal hormones. Therefore, it is recommended as an alternative choice for improve the prognosis of gastric cancer operation.

2. Introduction

Currently, the global morbidity and mortality of gastric cancer are threatening the health and life of people around the world. About 800,000 people died of gastric cancer each year and China accounted for 35% 1. Surgery is still the main therapy for gastric cancer. However, it is inevitable that the digestive tract is pulled and the peripheral gastric nerve partially cut off during the surgery, which lead to the increased sympathetic excitability and vagal nerve inhibition. Therefore, increased inhibitory neurotransmitters were released, resulting in weakened myoelectric activity. Besides, gastric antrum and partial duodenum resection could cause hormone secretion disorders in the stomach and small intestine, which further impacts the recovery of gastrointestinal function of patients [2].

Common intervention for gastrointestinal dysfunction after gastric cancer surgery consists of symptomatic treatment, lacking early

initiative and effective intervention [3]. In addition, the prokinetic western medicine including methoxyclopramide (MCP), domperidone (DOM), mosapride and itopride are frequently used for the treatment of gastrointestinal disorders [4-6]. Their clinical use can be limited by the potential harm such as the extrapyramidal symptoms of MCP and heart injury of DOM to some degree [4]. Particularly, none of the currently used medicine is found to be able to restore the nutritional and immunologic condition of the patients. Since traditional Chinese medicine has been reported to have better efficacy in treating functional dyspepsia compared with conventional gastrointestinal motility-related drugs, it may have promising potential trying traditional Chinese medicine in promoting operation induced gastrointestinal disorders [7].

Previously, we showed that Qihuang decoction, one traditional Chinese medicine, could restore the intestinal immune barrier and improve the mechanical barrier of the intestinal mucosa in rats after gastrectomy [8]. More importantly, it could effectively improve the nutrition and immune status of patients [9]. A nonnegligible phenomenon is that the stomach and colon are usually paralyzed in the early stage after radical gastrectomy due to anesthesia and surgical trauma. Oral administration of Chinese medicine at this point will have serious consequences to some extent, therefore, early direct intestinal instillation of Qihuang decoction was adopted on account of the persisted electrophysiological activity of the small intestine even after gastrectomy. The therapeutic effect of medicine instillation into the small intestine is limited by different factors such as concentration, temperature, speed and volume. After several years' exploration, we found that maintaining the temperature at 38-39°C and the speed of 30-40ml/min was an optimal implementation condition for intestinal instillation. Despite the finding that Qihuang decoction can promote the recovery of intestinal immune barrier and immune function [8, 9], the effect of Qihuang decoction on gastrointestinal dysfunction is still not systematically studied, especially on gastrointestinal motility and secretory function. This present study was thus designed to explore the effect of early direct intestinal instillation of Qihuang decoction on gastrointestinal motility and secretory function in patients after gastrectomy.

3. Materials and Methods

3.1. Study Design: The randomized controlled clinical study was conducted in the First Affiliated Hospital of Anhui University of Chinese Medicine and complied with the Helsinki Declaration. All participants had signed the written consent to participate the study after being informed in detail about the study procedures. A total of 272 patients that underwent gastrectomy were selected from January 1, 2015 to June 30, 2019. They were randomly divided into two groups (1:1) by a random number table (generated by SPSS 21.0) combined with the envelope method.

The diagnostic criteria coincided with the standards of the 5th edition of the "Guidelines for the Treatment of Gastric Cancer" issued in 2018 [11]. Staging criteria for gastric cancer was based on the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) 8th edition pathological tumor-node-metastasis (pTNM) [12].

3.2. Inclusion Criteria and Exclusion Criteria

Inclusion criteria were as follows: Patients with gastric cancer diagnosed by gastroscopy and pathological examination who need surgical treatment while without chemotherapy in the past 180 days. Exclusion criteria were listed as: patients with gastrointestinal dysfunction, abnormal liver function, intestinal absorption, metabolic disorders, immune dysfunction, or digestive system diseases, patients with severe malnutrition (BMI < 18 kg/m2), pregnant and lactating women, patients with severe accompanying diseases such as chronic cardiopulmonary insufficiency and chronic renal failure, patients underwent a cerebral infarction within 6 months, patients with distant metastases confirmed during the surgery.

3.3. Preoperative Preparation

Both groups received the same preparation before surgery. Specifically, they were banned for water and food for 24 hours, and were given oral catharsis medication of diarrhea for preoperative bowel preparation 8 hours before surgery. Subsequently, the antibiotics suitable for patients were used 30 minutes before surgery to prevent postoperative abdominal infection. Then a jejunal nutrition tube (Fuerkai Nasogastric tube, YZB/Su0943-2014, Nutricia Pharmaceuticals Wuxi Co., Ltd.) was inserted into the side hole of the lowermost section of the gastric tube, followed by the two tubes inserted into the stomach cavity (with a depth of 60 cm) through the nostril of the patient and fixed separately (Figure 1a). The gastric juice could be extracted from the tubes by the syringe.

4. Methods of Operation and Intraoperative Placement of Nutrient Tube

In this research, total gastrectomy, proximal gastrectomy and distal gastrectomy were selected as surgical methods. The anastomotic method was selected by Billroth Ⅱ or Roux-en-Y according to the actual situation. Before surgical anastomosis, the gastric tube was separated from the jejunal nutrition tube, and the nutrient tube was dragged and placed at the lower end of the anastomotic site, and the gastric tube was kept at the residual stomach or the upper end of the anastomotic site (Figure 1b). Drainage tubes were routinely placed in the abdominal cavity before abdominal closure, and the abdomen was closed layer by layer. Postoperative deep vein catheterization was performed in the patients.

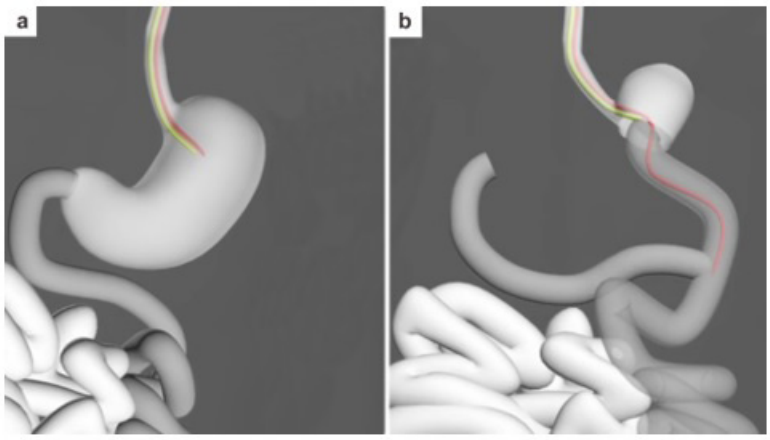

Figure 1: The diagram of the location of the gastric tube (yellow) and the nutrition tube (red) in patients. (a) Before the operation, the gastric tube and nutrient tube were inserted into the stomach cavity through the nostril. (b) After the operation, the position of the gastric tube remained unchanged while the nutrient tube was placed in the small intestine cavity.

4.1. Postoperative Treatment

The patient received parenteral nutrition (TPN) treatment within 24 hours when the gastrointestinal function was not recovered. Specifically, 2000-2500ml liquid was supplied by the intravenous infusion with a dose of 40 kcal/kg/d, which contains compound amino acid injection, 20% medium and long chain fat milk injection and the 5% glucose injection. Simultaneously, conventional treatment of electrolytes, vitamins, and trace elements were supplied.

24 hours after operation, the patients were randomly assigned to receive Enteral Nutrition (EN) for 7 days as follows:

(1) Control group

The temperature of the enteral nutrition emulsion (TPF, National Pharmaceutical Standard H20040188, Huarui company, total energy of 750 kcal per 500 ml liquid containing 28 g protein, 29 g fat, 94 g carbohydrates, 10 g dietary fiber and various minerals, vitamins) was maintained at 38-39 °C and injected through the jejunal nutrition tube with the speed from 10-20 drops/min to 40-60 drops/min according to the patients' reaction. The nutrient support scheme in control group was as follows: 100 ml saline was given on the 16th hour after surgery, then 250 ml TPF and 500 ml saline were given on the 1st day, 500 ml TPF and 250 ml saline were given on the 3rd to 4th day, 1000 ml TPF was given on the 5th day and 1500 ml TPF was given on the 6th to 7th day. On this basis, extra TPN was performed to reach a total energy of 30 kcal/kg/d for each patient.

(2) Research group

117g Qihuang decoction was composed of 20g Astragalus membranaceus, 20g Rheum officinale, 20g rhizome of largehead atractylodes, 10g Codonopsis pilosula, 10g Fructus aurantii immaturus, 10g Magnolia officinalis, 12g Salvia miltiorrhiza and 15g Radix Scutellariae. Then Qihuang decoction was mixed with 500mL water and boiled for 30 min. 300mL liquid medicine was preserved at 4°C for further clinical use. On the 24th hour after surgery, 150 ml of the Qihuang decoction extract was rewarmed to the temperature of 38-39°C and nasally fed into the intestine twice a day. The administration period of Qihuang decoction treatment lasted for 7 days.

4.2. Outcome Assessments

After the treatment of 7 days, the recovery time for resuming peristaltic sound, exhaust time, recovery time of anal defecation, and time of resume oral intake were recorded. Each patient received the abdomen auscultation in four abdominal regions every 4 hours postoperatively. The recovery of bowel sounds was confirmed once three times or more of the sound be heard within one minute, and the earliest time (h) was recorded.

In addition, the patient firstly underwent routine chest and abdominal dialysis to exclude the relevant contraindications of angiography. Then the gastrointestinal radiography was performed at the 1st, 2nd, and 4th hour on the 4th day after oral administration of meglumine diatrizoate to determine the location and the time of contrast agent arrival.

The gastrointestinal hormone was detected by collecting 4 ml peripheral venous blood of the patient under fasting state on preoperative day and the postoperative 3rd, 7th, 14th day in the morning. The plasma was acquired by centrifuging at 4000 r/min for 15 minutes (Sigma, GERMANY) within 12 hours upon collection. Afterwards, they were stored at –80°C for further use. The content of each hormone was measured by radioimmunoassay method on the radioimmunoassay apparatus (SN-694B, Shanghai Institute of Atomic Energy, Chinese Academy of Sciences).

The classification criteria of the postoperative complications of gastrectomy was referred to the "Japanese Clinical Oncology Research Group Classification Criteria for Postoperative Complications of Gastric Cancer" [13]. The occurrence of complications of grade Ⅱ or above was defined as the arise of complications while no complications occurred if it met the grade I or nothing happened.

4.3. Statistical Analysis

SPSS 21.0 (SPSS Inc, Chicago, IL, USA) statistical software was used

for data analysis. The normal data was expressed as means ± SD, if it conformed to homogeneity of variance, otherwise, it was expressed as median (interquartile range). The student t-test or Mann-Whiney U test were used for comparison between two groups, and repeated measures analysis of variance or Friedman rank sum test were used for multiple sets of three or more groups data analysis. For constituent ratio index comparison, the data was expressed as the number of cases or percentage, chi-square test or Fisher's exact test probability were applied, $P<0.05$ was considered to indicate statistical significance.

4.4. Ethical Considerations

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine (2020AH-13).

5. Results

5.1. Baseline Characteristics

In total, 260 participants were randomly divided into two groups with 132 patients in research group and 128 patients in control group. Fig. 2 is a flow diagram that summarizes participant screening, randomization and enrollment. There is no significant difference in the baseline characteristics of participants between the control group and the research group. Besides, basic diseases, pathologic types, pathological stage (pTNM), histological grading, surgical method, surgical time, and bleeding volume of patients were not significantly different between the two groups ($P>0.05$) (Table 1).

Table 1: Baseline demographics and clinical characteristics of patients.

Characteristic	Control group (n=128)	Qihuang decoction group (n=132)	$t/\chi^2/Z$	P
Gender [n(%)]			1.202	0.273
Male	105 (82.0)	101 (76.5)		
Female	23 (18.0)	31 (23.5)		
Age (years)	66.91 ± 9.17	65.24 ± 11.33	-1.303	0.194
Basic disease [n(%)]				
Hypertension	22 (17.2)	31 (23.5)	1.588	0.208
Diabetic	19 (14.8)	25 (18.9)	0.775	0.379
Pathological type			0.609	0.894
Adenocarcinoma	98	101		
Squamous carcinoma	14	13		
Adenosquamous carcinoma	9	8		
Other	7	10		
Pathological stage(pTNM)[a]			-0.564	0.573
Stage Ⅰ	35 (27.3)	40 (30.3)		
Stage Ⅱ	43 (33.6)	45 (34.1)		
Stage Ⅲ	41 (32)	37 (28)		
Stage Ⅳ	9 (7.1)	10 (7.6)		
Histological grading[a]			-0.981	0.326
Low differentiated	52 (40.6)	63 (47.8)		
Moderately differentiated	51 (39.8)	45 (34.1)		
High differentiated	25 (19.6)	24 (18.1)		
Surgical method			0.509	0.775
Proximal gastrectomy	10 (7.8)	8 (6.1)		
Distal gastrectomy	34 (26.6)	39 (29.5)		
Total gastrectomy	84 (65.6)	85 (64.4)		
Operation time [M(Q),min]	208.0(211.0-217.0)	213.5(207.0-220.0)	0.735	0.463
Bleeding volume (ml)	217.34 ± 8.17	215.35 ± 23.27	-0.926	0.356

Note: Data were expressed as mean ± SD or n (%) or M (QL-QU).

a: The AJCC / UICC 8th edition of gastric cancer pTNM staging in 2016.

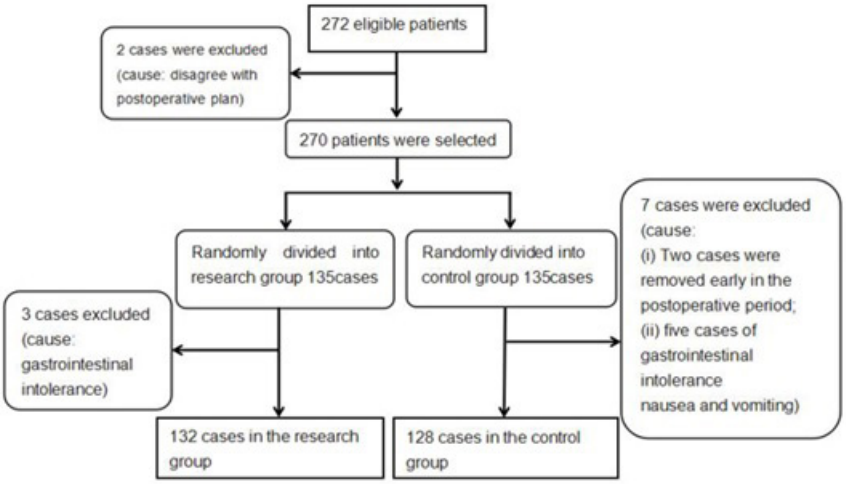

Figure 2: The flow diagram of participant screening, randomization and enrollment.

5.2. Comparison of Gastrointestinal Motility Between Two Groups

After the treatment of Qihuang decoction for 7 days, the recovery time of resuming peristaltic sound, anal exhaust time, recovery time of anal defecation, and time of resume oral intake were significantly improved in the Qihuang decoction group compared with control group (P<0.001, P<0.001, P<0.001, P<0.001, respectively) (Figure 3).

Furthermore, the time of meglumine diatrizoate reaching ileocecal junction and rectum were detected by gastrointestinal radiography. In Qihuang decoction group, 114 patients took meglumine diatrizoate to the ileocecal junction for less than 4 hours, and 18 patients were more than or equal to 4 hours. And in control group, 75 patients took meglumine diatrizoate to the ileocecal junction for less than 4 hours, and 53 patients were more than or equal to 4 hours (P<0.01). As for the time for diatrizoate meglumine to reach the rectum, 55 patients took less than 4 hours, and 77 patients took 4 hours or more in Qihuang decoction group. While in control group, 31 patients took less than 4 hours, and 97 patients took 4 hours or more. This result also showed that Qihuang decoction can promote the recovery of gastrointestinal motility (P<0.05) (Figure 4).

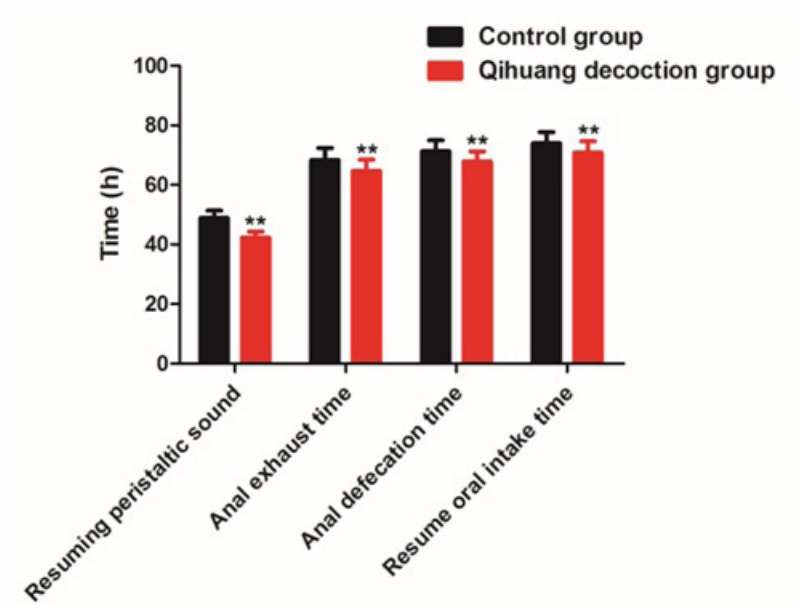

Figure 3: The recovery time of gastrointestinal motility. Compared with the control group ** P<0.01.

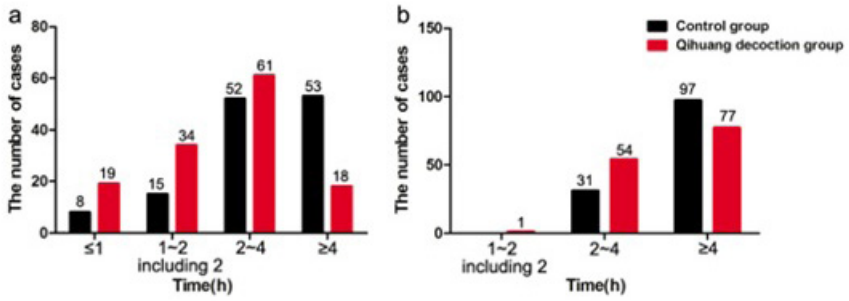

Figure 4: The results of gastrointestinal radiography. a: the number of cases of meglumine diatrizoate reaching ileocecal junction at different time. b: the number of cases of meglumine diatrizoate reaching rectum at different time.

5.3. Changes of Gastrointestinal Hormones Between Two Groups

The gastrointestinal function is largely influenced by the balance of the hormones that promots and inhibits gastrointestinal motility, and the hormones can affect gastrointestinal function by paracrine or directly acting on target cells. We therefore compared the level of hormones MOT, GAS, CCK that accelerate gastrointestinal movement and GIP, VIP, and SS that suppress gastrointestinal movement. The hormones were reduced on the 3rd day after operation and then gradually increased except VIP in two groups, and the hormones showed a similar tendency between two groups. In control group, the level of MOT, GAS, and CCK on the 14th day after operation were significantly lower than before operation, and GIP, VIP, and SS were significantly higher than before operation (P<0.05). While in Qihuang decoction group, the level of MOT, GAS, and CCK on the 14th day after operation is comparable or even higher compared with that of before operation.

For hormones that promote gastrointestinal motility, the level of GAS and MOT significantly increased on the 3rd, 7th, 14th day after operation in Qihuang decoction group compared with control group (P<0.05). But the significant increasement of CCK was only observed on the 14th day after operation in Qihuang decoction group than control group (P<0.05). In terms of hormones that inhibit gastrointestinal motility, the level of GIP, VIP and SS on the 3rd, 7th, 14th day after operation in Qihuang decoction group were significantly decreased than control group (P<0.05) (Figure 5).

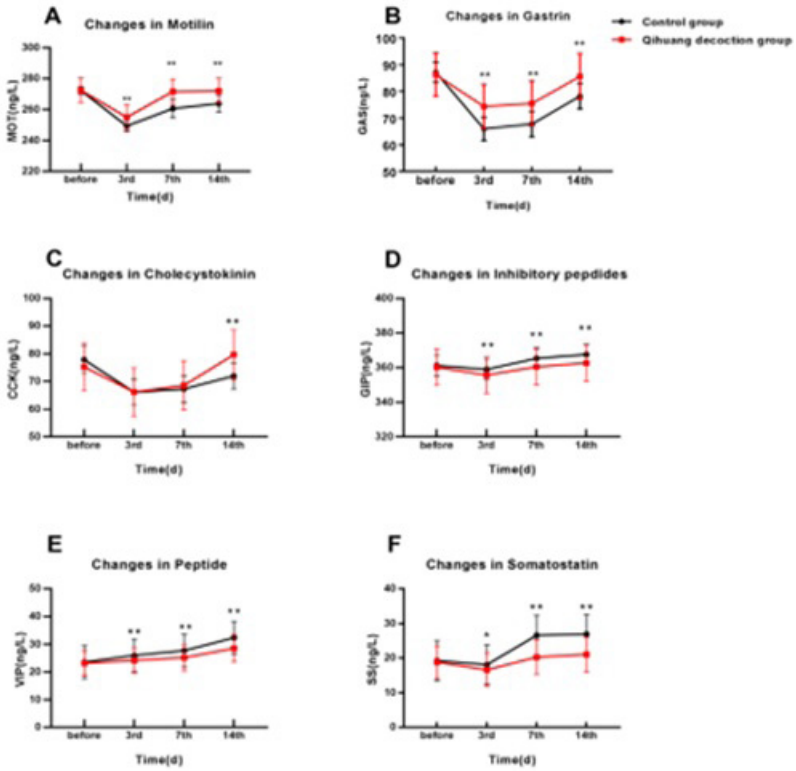

Figure 5: The changes of gastrointestinal hormones in the two groups after gastric cancer surgery, among which the red line represented Qihuang decoction group and the black line represented control group. A~F indicated the change of the hormones MOT, GAS, CCK, GIP, VIP, SS at different time respectively. Compared with the control group * P<0.05 and ** P<0.01.

5.4. Postoperative Complications

The total incidence of postoperative complications after gastrectomy was 27.69% including intestinal obstruction, anastomosis leakage, postoperative bleeding and other adverse complications. In particular, the incidence of complications in Qihuang decoction group and control group was 12.88% and 43% respectively (P<0.001). Among them, the incidence of complications such as intestinal obstruction, infection-related diseases and gastroparesis in Qihuang decoction group were significantly lower than control group (P<0.05). It is worth noting that in the control group, there was 1 case of early death and 1 case of thrombosis-related diseases, and none of these occurred in Qihuang decoction group (Table 2).

Table 2: The incidence of complications in the Qihuang decoction group and control group

Complications	Control group (n=128)	Qihuang decoction group (n=132)	Total (n=260)	χ^2	*P*
Intestinal obstruction	9 (7.03)	2 (1.52)	11 (4.23)	4.483	0.034
Anastomosis leakage	6 (4.69)	4 (3.03)	10 (3.85)	0.447	0.504
Postoperative bleeding	3 (2.34)	2 (1.52)	5 (1.92)	0.228	0.633
Adverse event					
Infection-related	12 (9.40)	2 (1.52)	14 (5.38)	7.076	0.008
Poor incision healing	16 (12.50)	6 (4.55)	22 (8.46)	4.481	0.034
Thrombosis-related	1 (0.78)	0 (0.00)	1 (0.38)	1.027	0.311
Early death	1 (0.78)	0 (0.00)	1 (0.38)	1.027	0.311
Gastroparesis	7 (5.47)	1 (0.76)	8 (3.08)	4.547	0.033
Total	55 (43.00)	17 (12.88)	72 (27.69)	16.811	0

Note: Data were expressed as n (%).

6. Discussion

Gastrointestinal motility disorder normally refers to mechanical obstruction such as residual gastric weakness, delayed emptying, slow intestinal peristalsis, anastomosis deficiency or jejunum output disorders [14]. Due to different factors such as surgical anesthesia, anatomical and physiological changes, traumatic inflammation and postoperative gastrointestinal hormone changes, gastrointestinal function is often inhibited after abdominal surgery, which not only affects nutrients absorption, but also furtherly aggravate to gastrointestinal failure and may even cause systemic inflammatory response syndrome, sepsis and multiple organ dysfunction syndrome [15, 16]. We therefore demonstrated that Qihuang decoction, a traditional Chinese medicine, was beneficial to restore gastrointestinal motility function by regulating the secretion of gastrointestinal hormone, furthermore, the incidence of adverse complications were largely reduced.

The evaluation of gastrointestinal dysfunction was often assessed by the time of eating, the recovery time of bowel sounds, the time of anal exhaustion and defecation in patients after gastric cancer treatment. To acquire a more objective result in the present study, gastrointestinal peristalsis inferred from gastrointestinal radiography in which the contrast agent's excretion process from esophagus to rectum was recorded. Both the time result and the location of diatrizoate meglumine showed that Qihuang decoction significantly improved the gastrointestinal function. Here, the used contrast agent diatrizoate meglumine not only stimulated intestinal peristalsis, but also reduced anastomotic edema [17]. Another traditional herbal medicine, Daikenchuto, was previously demonstrated to promote the gastrointestinal motility disorder. After careful comparison of the time of exhaust and defecation, it seemed that Qihuang decoction played a greater role in promoting gastrointestinal motility after gastrictomy [18], deserving more attention in the related field of traditional Chinese medicine treatment in the near future.

The gastrointestinal hormones are highly efficient peptides secreted by special endocrine cells [19]. Among them, MOT, GAS and CCK were commonly seen as hormones promoting gastrointestinal body contraction and accelerating gastric emptying [20-22], while GIP, VIP and SS were considered as the inhibitory hormones [23-25]. It was well known that Enteral Nutrition (EN) was more recommended for postoperative recovery compared with Parenteral Nutrition (PN), until recently, scholars found that the easily recovered levels of MOT and CCK in EN treated patients might be the underlying cause [26]. Therefore, we speculate that the levels of hormones might be the significant elements affecting the recovery of gastrointestinal function. Our results showed that gastrointestinal hormone levels fell to the minimum on the third day, coincided with the obviously decreased gastric motility, which may be related to the impaired recovery induced by surgical removal of the gastric antrum and part of the duodenum. Besides, the changed inherent environment of the gastrointestinal tract also contributed to inhibiting the secretion of gastrointestinal hormones after the anesthesia and laparotomy. The hormone levels in both groups increased gradually after three days, and we showed that the hormones like MOT, GAS and CCK increased while GIP, VIP and SS decreased after Qihuang decoction treatment. Similarly, another Chinese medicine, Simo decoction effectively promoted the recovery of gastrointestinal function after gynecological abdominal surgery, which might strongly corelated with the recovery of hormones Growth hormone-releasing peptide (GHRP-GHrelin)

and MOT [27]. Besides, it was found that Liwei huchang decoction could improve the thickness of gallbladder wall by promoting the recovery of GAS and MOT after laparoscopic gallbladder preservation and lithotomy [28]. All these indicated the levels of hormones are essential for normal gastrointestinal function maintenance.

Clinically, postoperative complications of gastrectomy mainly include postoperative bleeding, anastomotic leakage, pancreatic leakage, intestinal obstruction, and the adverse events evolving intestinal obstruction, incision healing, gastric emptying disorders, and infection [29], which greatly impact the prognosis once they appeared. In this study, the total incidence of complications was 27.67%, similar to other domestic and foreign studies [30, 31]. Noticeably, the incidence of complications and adverse events in the Qihuang decoction group was significantly lower than that in the control group, which may be caused by the nutritional and immune action of Qihuang decoction previously demonstrated by our team [8]. In addition, fewer complications occurred in the Qihuang decoction group compared with the reported herbs, Daikenchuto [17]. Moreover, the rates of complications were not worse than currently widely used drugs like Itopride and mosapride after careful analysis [5, 6]. Hence, our experience of early Qihuang decoction intervention (within 24 hours after surgery) not only improve the quality of life but also ensure the safety.

7. Conclusion

In conclusion, Qihuang decoction, one traditional Chinese medicine, exerted beneficial influence on gastrointestinal motility and secretory function after gastrectomy. Particularly, the incidence of operation associated complications reduced after early intervention of Qihuang decoction. Owing to the nutritional and immunomodulation action, early clinical use of Qihuang decoction was strongly recommended after gastrectomy. Nevertheless, further clinical comparison of gastrointestinal function between Qihuang decoction treatment and similar western medicine or traditional Chinese medicine treatment is strongly recommended, and the definite mechanisms of Qihuang decoction in promoting gastrointestinal function need more clarification.

8. Funding

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