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*Randomized Clinical Trial*

**Improvement of inflammatory response and gastrointestinal function in perioperative of cholelithiasis by Modified Xiao-Cheng-Qi decoction**

Sun BF *et al.* Effects of MXD

## **Abstract**

### **BACKGROUND**

In the perioperative period of biliary surgery, various factors can induce the release of a large number of inflammatory factors, leading to an imbalance in pro-inflammatory and anti-inflammatory responses and resulting in gastrointestinal (GI) dysfunction. Enhanced Recovery After Surgery protocols in biliary surgery have been shown to reduce the stress response and accelerate postoperative recovery. It is crucial to reduce the inflammatory response and promote the recovery of GI function after biliary surgery, both of which are the basis and key for perioperative care and postoperative recovery.

### **AIM**

To better understand the effects of Modified Xiao-Cheng-Qi decoction (MXD) on inflammatory response and GI function in the perioperative management of cholelithiasis and their correlation.

### **METHODS**

This was a prospective randomized placebo-controlled trial, in which 162 patients who received biliary tract surgery were randomly assigned to three groups: MXD group, XD group, and placebo-control group. The observed parameters included frequency of bowel sounds, time of first flatus and defecation, time of diet, and amount of activity after surgery. The serum levels of C-reactive protein (CRP), interleukin (IL)-6, IL-10, serum amyloid A protein (SAA), and substance P were measured by the enzyme-linked immunosorbent assay. Then, the spearman correlation coefficient was used to analyze the relationship between the indicators of GI function and inflammation.

### **RESULTS**

Compared to the placebo-control, improvements in GI function were observed in the MXD groups including reduced incidence of nausea, vomiting, and bloating; and earlier

first exhaust time, first defecation time, and feeding time after surgery ( $P < 0.05$ ). On the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery, IL-6, CRP and SAA levels in MXD group were lower than that in placebo control, but substance P level was higher, compared to the control ( $P < 0.05$ ). Functional diarrhea occurred in both MXD and XD groups without any other adverse effects, toxic reactions, and allergic reactions. Diarrhea was relieved after the discontinuation of the investigational remedies. Bowel sounds at 12 h after surgery, the occurring time of the first flatus, first defecation, postoperative liquid diet and semi-liquid diet were significantly correlated with levels of IL-6, CRP, SAA and substance P on second day after surgery ( $P < 0.05$ ).

## CONCLUSION

Treatment with MXD can relieve inflammatory response and improve GI function after surgery. Moreover, there are significant correlations between them. Furthermore, it does not cause serious adverse reactions.

**Key Words:** Modified Xiao-cheng-qi Decoction; Cholelithiasis; Inflammatory response; Gastrointestinal function; Enhanced Recovery After Surgery; Perioperative

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**Core Tip:** It is crucial to reduce the inflammatory response and promote the recovery of gastrointestinal (GI) function after biliary surgery, as both are the basis and key for perioperative care and postoperative recovery. Treatment with Modified Xiao-Cheng-Qi decoction can reduce the inflammatory response and improve GI function after surgery. Moreover, a close correlation between them was found in our study. Our findings provide insights into the possible role of inflammatory stress response in the pathogenesis of postoperative GI tract dysfunction (PGID) and support the

development of novel therapeutic strategies for the prevention and treatment of postoperative inflammatory stress response and PGID.

## **INTRODUCTION**

In the perioperative period of biliary surgery, various factors such as starvation, tissue injury, anesthesia, and pain can induce the release of a large number of inflammatory factors, leading to an imbalance in pro-inflammatory and anti-inflammatory responses and result in gastrointestinal (GI) dysfunction<sup>[1-7]</sup>. Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing the profound stress response following surgery<sup>[8-11]</sup>. ERAS protocols in biliary surgery have been shown to reduce the stress response and accelerate postoperative recovery<sup>[12-14]</sup>. It is crucial to reduce the inflammatory response and promote the recovery of GI function after biliary surgery, both of which are the basis and key for perioperative care and postoperative recovery<sup>[15-17]</sup>. Therefore, it is necessary to develop novel interventions to reduce the inflammatory response and improve the recovery of GI function after biliary surgery. However, the relationship between inflammatory response and postoperative GI tract dysfunction (PGID) is complex and also there is less report on the correlation between the inflammatory response and GI function recovery after biliary surgery.

Modified Xiao-Cheng-Qi decoction (MXD) is a new remedy with traditional Chinese medicine (TCM), which has the addition of Huangqi (Astragalus), Ruxiang (Frankincense) and Moyao (Myrrh) compared to the classic XD. It is notable that MXD was primarily designed by the author based on the characteristics of biliary tract surgery, which have been applied to therapy according to “clinical differentiation” for several years. To better understand the effects of MXD on the inflammatory response and GI function recovery in perioperative of cholelithiasis, also their correlation, we conducted this prospective randomized controlled study.

## **MATERIALS AND METHODS**

### *Study design*

This study was a prospective randomized, double-blind, and placebo-controlled trial. In this study, three treatment groups were randomized in a 1:1:1 ratio (test:control:control). To obtain statistically significant results, the estimated sample size in both the test group and control group was at least 45 patients per group, according to ERAS. Participants were stratified according to the presence or absence of common bile duct stones. Considering the possibility of dropping out of the trial (10%), at least 50 patients were needed in each group, *i.e.*, our study needed a total of 150 patients in the three groups. Actually, 185 patients were assessed for eligibility, and finally 170 patients were recruited during the period from January 2017 to January 2018. All participants were randomly assigned to the three groups (MXD, XD, and control). Among them, 162 subjects (95.3%) finally completed the treatment. Four patients in the MXD group and four in the XD group dropped out because they could not tolerate the taste of the TCM or were unwilling to complete this study. The reasons and dates of withdrawal were recorded in detail. The general situation and indicators of those patients were also evaluated. A flow diagram of the patient enrollment and study phase schedule was shown in Figure 1.

The study procedures were approved by the ethics committee of Binzhou Medical University Hospital [No. Ethical research (2017-026-01)]. This study was registered at the Chinese Clinical Trial Registry (ChiCTR2000033125). The statistical methods of this study were reviewed by Qiang-Pu Chen from Binzhou Medical University Hospital. An investigator who was unaffiliated with this study created the randomization list. The randomization was completed by SAS 9.4 software to generate a random sequence. The participants were randomly allocated at a 1:1:1 ratio to three groups: (1) MXD group: ERAS + MXD [Dahuang (rhubarb) 6 g, Houbu (*Magnolia officinalis*) 6 g, Zhishi (Immature Bitter Orange) 12 g, Huangqi (*Astragalus*) 20 g, Ruxiang (Frankincense) 6 g, Moyao (Myrrh) 6 g]; (2) XD group: ERAS + XD [Dahuang (rhubarb) 6 g, Houbu (*Magnolia officinalis*) 6 g, Zhishi (Immature Bitter Orange) 12 g]; and (3) Placebo-control group: ERAS + warm water (Table 1). All patients underwent ERAS protocol

during the perioperative period. Rhubarb, *Magnolia officinalis*, Immature Bitter Orange, Astragalus, Frankincense and Myrrh are Chinese Medicine Granules and all produced by Yifang Pharmaceutical Corporation (Guangdong, China). For one dose of MXD or XD, all herb ingredients were extracted with 100 mL warm boiled water to make an aqueous extract. Then 50 mL of investigational drug was administered orally at 14-16 and 6-8 h before surgery; and at 6-8, 14-16, 22-24, and 30-32 h after surgery. The control group was given 50 mL warm water at the same time.

#### ***Inclusion and exclusion criteria***

The inclusion criteria were: confirmed diagnosis of cholelithiasis, surgical indications; written informed consent for surgery; underwent elective laparoscopic choledocholithotomy and cholecystectomy or laparoscopic cholecystectomy; > 18 years and ≤ 75 years; had no severe cardiopulmonary complications and American Society of Anesthesiologists grade (ASA) I or II; and underwent primary biliary tract surgery. Exclusion criteria were: Patients with acute inflammation, fever, or other diseases that might seriously impact the body's stress and inflammatory responses, accompanied by immune diseases, metabolic diseases, or use of some drugs that affect the immune system; ≤ 18 years and > 75 years; had undergone an emergency operation; had undergone reoperation of the biliary tract; had severe cardiopulmonary complications; or ASA III or IV. Randomization was achieved by a computer-generated list of numbers for group allocation.

#### ***ERAS protocols***

The ERAS protocols were implemented as follows: (1) Preoperative preparation included admission education, nutritional risk screening, disease assessment, detailed introduction of the treatment plan, preemptive analgesia, Visual Analogue Scale (VAS) pain score; (2) Intraoperative management included sedative analgesia before anesthesia, general anesthesia, intraoperative warming, controlled infusion, and minimally invasive surgery; and (3) Postoperative management included postoperative

continuous monitoring of vital signs, VAS pain score, early ambulation, early diet, postoperative analgesia, and health guidance before discharge.

### *General anesthesia*

General anesthesia was performed by one of six trained surgeons, who had at least 5 years of experience. Patients were assigned to each anesthesia group by the random number table. When the procedure began, the peripheral vein was opened, and the patients' electrocardiogram, heart rate, and blood oxygen saturation were monitored routinely. Anesthesia induction was performed by intravenous injection of propofol 1.5-2.5 mg/kg, fentanyl 2-3 µg/kg, and atracurium besylate 0.3-0.6 mg/kg. Mechanical ventilation was also performed after tracheal intubation. The conditions for mechanical ventilation were as follows: Tidal volume, 8-12 mL/kg; positive end-expiratory pressure ventilation, 2-4 cm H<sub>2</sub>O; ventilation frequency, 12-20 times/min; inspired oxygen concentration, 30-60%; gas flow rate, 2 L/min; and end-tidal partial pressure of carbon dioxide, 35-45 mmHg. The nasopharyngeal temperature probe was used to monitor the patient's intraoperative temperature. Meanwhile, the thermal insulation blanket and infusion heater were used to keep the patient warm during the operation. To anesthetize the patients, remifentanyl (0.25-0.5 µg/kg min) was infused intravenously and sevoflurane was inhaled. It is notable that the inhalation concentration was adjusted according to the patients' vital signs. During the operation, atracurium besylate 0.05 mg/kg was injected intravenously, meanwhile anesthesiologists performed radial artery catheterization to continuously monitor the invasive blood pressure. At that time, anesthesiologists also performed right central venous catheterization to continuously monitor the pressure of the central vein, guide fluid input, maintain hemodynamic stability, and administer vasoactive drugs when necessary. Respiratory parameters were adjusted according to the results of the blood gas analyses.

### *Operation mode*



Biliary surgery was performed by one of four trained surgeons, each of whom has at least 10 years of experience. Patients were assigned to each surgical group by the random number table. The general tasks included checking the status of patients before surgery, disinfecting patient's skin, and laying sterile sheets on the skin. A small arc-shaped incision of about 1.5 cm in length was made under the umbilicus, and then a pneumoperitoneum needle was inserted into the abdominal cavity. Carbon dioxide gas was injected into the pneumoperitoneum to 15 mmHg, followed by insertion of a 10 mm trocar into the abdominal cavity through direct trocar puncture and laparoscopy to explore the abdominal cavity. Two more cannulas were used to puncture under the xiphoid process, the intersection of the right costal margin and the middle clavicular line. Another trocar was inserted under the intersection of the right costal margin and axillary line under laparoscopic surveillance if needed. Laparoscopic choledocholithotomy and cholecystectomy were performed in patients with choledocholithiasis and cholecystolithiasis, while laparoscopic cholecystectomy was done in patients with cholecystolithiasis. The abovementioned patients were randomly assigned to each group according to the mode of operation.

### ***Outcome measures***

The outcome measures were: The frequency of bowel sounds, time of first flatus and defecation, time of drinking and eating, and the amount of activity after surgery. The frequency of bowel sounds was observed at 2 h before surgery and at 0, 6, 12, and 24 h after surgery. Thus, stethoscope was performed for 2 min at several points, including McBurney point, anti McBurney's point, and 5 cm below the left and right costal margin; thus, the quality of intestinal sound was recorded. The mean value was calculated and recorded. The time to first passage of flatus, first defecation, first postoperative drinking time, first postoperative liquid diet time, first postoperative semi-liquid diet time, and first postoperative normal diet time were recorded in detail. Physical activity time and distance were assessed using the Mi Band activity monitor

(MB4; Xiaomi Technology Co., Ltd., Beijing, China) on days 1, 2, 3, 4, and 5 (from 08:00 to 08:00) after surgery.

The complications were also monitored based on “Evidence-based clinical practice guidelines for cholelithiasis 2016”<sup>[18]</sup> and “Nurse’s guide to common postoperative complications”<sup>[19]</sup>. Incision complications include surgical site infections, dehiscence, seromas, and hematomas<sup>[20]</sup>. Intra-abdominal infection is a common disease process after operation, which is associated with substantial morbidity and death<sup>[21]</sup>. Deep-vein thrombosis is a condition in which a blood clot forms in a deep vein and causes a blockage<sup>[22]</sup>. Bile leakage originates from the cut surface of the liver, from injury of the bile ducts, or from anastomotic leakage after bilioenteric anastomosis<sup>[23]</sup>. Nausea is the unpleasant sensation of being about to vomit and is often associated with mouth watering. Vomiting is the forceful expulsion of gastric contents *via* the mouth<sup>[24]</sup>. Bloating has been defined as a feeling of increased abdominal pressure that may or may not be accompanied by objective abdominal distension, *i.e.*, visible enlargement of the waist<sup>[25]</sup>. In addition, the adverse reactions of TCM were observed in detail. Adverse drug reactions are described as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product”<sup>[26]</sup>.

A comparison of the serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), IL-10, serum amyloid A protein (SAA) and substance P among the three different groups was performed by the enzyme-linked immunosorbent assay at different time points, namely on the first day before surgery as well as on days 1, 2, and 5 after surgery. Besides, substance P is a member of the family of mammalian tachykinin peptides, which is predominantly released by enteric neurons, and exert a potent contractile effect on GI smooth muscle through tachykinin receptors by modulating ionic channels and by producing second messengers<sup>[27]</sup>.

### ***Statistical analyses***

SPSS software version 24.0 was used to analyze the data obtained from this study. The Pearson's chi-squared test was applied to categorical variables such as sex and operation type. Normality distribution of data was first determined by the Kolmogorov-Smirnov test and accordingly, groups were compared using one-way analysis of variance, student's *t*-test or Mann-Whitney *U* test. The spearman correlation coefficient was used to analyze the relationship between the indicators of inflammation and GI function.  $P < 0.05$  was considered statistically significant.

## **RESULTS**

### ***Baseline characteristics***

The protocol of this study was approved by the ethics committee of Binzhou Medical University Hospital (No. Ethical research 2017-026-01). All participants provided written informed consent. The basic characteristics of the patients in the three groups are described in Table 2, in which there were no significant differences among the three groups in age, sex, body mass index, concomitant disease, surgery type, operation time, or intraoperative blood loss ( $P < 0.05$ ; Table 2).

### ***Recovery of GI function after biliary surgery***

Our study found that there was a greater frequency of bowel sounds in the MXD and XD groups compared to the control group at 6, 12, and 24 h after surgery ( $P < 0.05$ ). There was a greater frequency of bowel sounds in the MXD group as compared to that in the control group at 0 h after surgery ( $P < 0.05$ ). The first exhaust time and first defecation time after surgery were earlier in both the MXD and XD groups compared to the control group ( $P < 0.05$ ; Table 3).

### ***Diet after biliary surgery***

Compared to the control group, the time of drinking water, liquid diet, and half-liquid diet in either the MXD group or XD group was shorter ( $P < 0.05$ ). After surgery, the

half-liquid diet time in the MXD group was shorter than that in the XD group ( $P < 0.05$ ; Table 4).

#### *Physical activity after biliary surgery*

On days 1 and 2 after surgery, the physical activity time and distance in the MXD group were greater than those in the XD group or control group ( $P < 0.05$ ). On day 3 after surgery, the practice time of physical activity of the patients in MXD group was longer than that in the control group, meanwhile, the activity distance of patients in the MXD group was much farther than that in both the XD and control groups ( $P < 0.05$ ; Table 5).

#### *Complications after biliary surgery*

Compared with the control group, the incidence of nausea, vomiting, and bloating in either the MXD group or XD group was reduced ( $P < 0.05$ ). There were no serious adverse reactions in the three groups (Table 6).

#### *Adverse reactions of the investigational remedy*

Functional diarrhea occurred in both MXD and XD groups without any other adverse effects, toxic reactions, and allergic reactions. The main symptoms of functional diarrhea were the increased fecal frequency ( $> 3$  times/d), increased fecal volume ( $> 200$  g/d), thin fecal quality ( $> 85\%$ ), and no abdominal pain ( $> 75\%$ )<sup>[28,29]</sup>. Based on these symptoms, the number of cases with diarrhea was counted. Diarrhea was relieved after the discontinuation of the investigational remedies. The incidence of diarrhea in the MXD group and the XD group was significantly higher than that in the control group on the 1<sup>st</sup> before surgery and 1<sup>st</sup>, 2<sup>nd</sup> d after surgery ( $P < 0.05$ ). There was no significant difference among the three groups on the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> d after surgery ( $P > 0.05$ ) (Table 7).

#### *Inflammatory indicators and substance P*

**IL-6:** On the 1<sup>st</sup>, 2<sup>nd</sup>, and 5<sup>th</sup> d after surgery, the serum concentrations of IL-6 in the three groups were higher than that on the 1<sup>st</sup> d before operation ( $P < 0.05$ ). It is notable that on the 1<sup>st</sup> d after surgery, the serum levels of IL-6 in both MXD and XD groups were lower than that in the control group ( $P < 0.05$ ). While, on the 2<sup>nd</sup> d after surgery, the serum level of IL-6 in MXD group was significantly lower than that in both XD group and control group ( $P < 0.05$ ). However, there was no statistical difference in the serum level of IL-6 between the three groups on the 1<sup>st</sup> d before surgery and 5<sup>th</sup> d after surgery ( $P > 0.05$ ) (Table 8).

**IL-10:** Compared with the 1<sup>st</sup> d before surgery, there was no statistically significant difference in the serum concentrations of IL-10 between the three groups on the 1<sup>st</sup>, 2<sup>nd</sup>, and 5<sup>th</sup> d after surgery ( $P > 0.05$ ). While there was also no statistical difference in the serum levels of IL-10 between the three groups on the 1<sup>st</sup> day before surgery and 1<sup>st</sup>, 2<sup>nd</sup>, and 5<sup>th</sup> d after surgery ( $P > 0.05$ ) (Table 8).

**CRP and SAA:** On the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery, the serum concentrations of CRP and SAA in the three groups were higher than that on the 1<sup>st</sup> d before surgery ( $P < 0.05$ ). It is notable that on the 5<sup>th</sup> d after surgery, the serum levels of CRP in the control group and SSA in MXD and XD groups were higher than that on the 1<sup>st</sup> d before surgery ( $P < 0.05$ ). On the 1<sup>st</sup> d after surgery, the serum levels of CRP and SAA in both the MXD group and XD group were lower than that in the control group ( $P < 0.05$ ), and the serum level of SAA in MXD group was significantly lower than that in the XD group ( $P < 0.05$ ). While on the 2<sup>nd</sup> d after surgery, the serum level of CRP in MXD group was lower than that in either the XD group or the control group ( $P < 0.05$ ), while SAA in the MXD group was lower than that in the control group ( $P < 0.05$ ). There was no statistically significant difference in the serum levels of CRP and SAA between the three groups on the 1<sup>st</sup> d before surgery and 5<sup>th</sup> d after surgery ( $P > 0.05$ ) (Table 8).

**Substance P:** On the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery, the serum concentration of substance P in the MXD group was higher than that on the 1<sup>st</sup> d before surgery ( $P < 0.05$ ). Our study also found that on the 1<sup>st</sup> d after surgery, the serum level of substance P in the MXD group was higher than that in both the XD and control groups ( $P < 0.05$ ). Moreover, on the 2<sup>nd</sup> d after surgery, the serum levels of substance P in the MXD and XD groups were higher than that in the control group ( $P < 0.05$ ; Table 8).

#### *Spearman correlation analysis between indicators of the inflammation and GI function*

In terms of correlations, bowel sounds at 12 h after surgery were significantly correlated with the levels of IL-6, CRP and SAA on the 2<sup>nd</sup> d after surgery ( $r = -0.25, -0.22, -0.33$ ;  $P \leq 0.001$ ,  $P \leq 0.001$ , and  $P \leq 0.001$ , respectively). The occurring time of the first flatus was correlated significantly with the levels of IL-6 and CRP ( $r = 0.20, 0.35$ ;  $P \leq 0.001$ ,  $P = 0.01$ , respectively). While the occurring time of the first defecation showed its correlation with CRP and SAA levels on the 2<sup>nd</sup> d after surgery ( $r = 0.30, 0.24$ ;  $P \leq 0.001$ ,  $P \leq 0.001$ , respectively). Similarly, the time of the postoperative liquid diet and the postoperative semi-liquid diet were correlated significantly with CRP levels on the 2<sup>nd</sup> d after surgery ( $r = 0.27, 0.29$ ;  $P \leq 0.001$ ,  $P \leq 0.001$ , respectively). In addition, the level of substance P and SAA on the 2<sup>nd</sup> d after surgery showed a significant correlation ( $r = -0.24$ ;  $P \leq 0.001$ ). Bowel sounds at 12 h after surgery, the occurring time of first flatus, and that of the first defecation were significantly correlated with substance P ( $r = 0.31, -0.23, -0.25$ ;  $P \leq 0.001$ ,  $P \leq 0.001$ , and  $P \leq 0.001$ , respectively). Other correlations were not significant (Table 9).

## **DISCUSSION**

In the perioperative period of biliary surgery, various injury factors can activate immune cells through different ways, such as damage-associated molecular patterns and pathogen-associated molecular patterns, and cause excessive release of pro-inflammatory factors, which then lead to local inflammatory response and participate in the body's defense response<sup>[10,11]</sup>. Moderate inflammatory response in the perioperative period is associated with the defense response and maintenance of homeostasis<sup>[30]</sup>.



However, in the case of an excessive inflammatory response, a large number of inflammatory cells are activated, resulting in a continuous inflammatory response and immune activation. The associated release of a large number of pro-inflammatory mediators<sup>[31]</sup> and the imbalance between pro-inflammatory mediators and anti-inflammatory mediators eventually lead to systemic inflammatory response syndrome and GI dysfunction<sup>[32-35]</sup>.

IL-6 is a main postoperative proinflammatory factor and a reliable predictor of systemic inflammatory response syndrome<sup>[36]</sup>, which is also positively correlated with the severity of surgical trauma<sup>[37]</sup>. In the randomized controlled trials, Wang *et al*<sup>[38]</sup> and Chen *et al*<sup>[39]</sup> confirmed that IL-6 was positively correlated with surgical trauma and acute inflammation, so that IL-6 can be used as a predictor of postoperative inflammatory response. Moreover, IL-10 can negatively regulate the inflammatory response and contributes to the maintenance of pro-inflammatory and anti-inflammatory homeostasis<sup>[40]</sup>. For example, Rahr *et al*<sup>[41]</sup> and Oldenburg *et al*<sup>[42]</sup> revealed that IL-10 may maintain the balance of inflammatory response. In this study, we found that the decrease of IL-6 after surgery in MXD group was more obvious than that in the control group, and the level of IL-10 was more stable before and after surgery. To some extent, MXD is helpful to reduce the inflammatory response, in order to maintain the balance of pro-inflammatory and anti-inflammatory. Except for the inflammatory response during surgical trauma, the body also synthesizes a large number of acute-phase proteins, which inhibit the release of proteolytic enzymes, cytokines, vasoactive substances, and repair damaged tissues<sup>[43]</sup>. Among the acute phase proteins, CRP and SAA are mainly regulated by cytokines, and their dynamic changes might reflect the degree of trauma and stress response<sup>[44,45]</sup>, so that both of them can be used as the main indicators for evaluating postoperative trauma, detecting septic shock and predicting organ failure<sup>[46]</sup>. Actually, Li *et al*<sup>[47]</sup> and Jung *et al*<sup>[48]</sup> confirmed by randomized controlled trials that CRP and SAA are positively correlated with the degree of trauma and stress response. In our study, the levels of IL-6, CRP and SAA on the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery were significantly higher than those before surgery. While their serum

level in MXD group was significantly lower than that in the control group. Taken together, MXD can reduce the response to postoperative inflammatory stress to some extent.

According to historical literature, XD was selected from “Treatise on Febrile and Miscellaneous Diseases” written by Zhang Zhong-Jing, a famous TCM doctor of the Han Dynasty in China. The composition of XD includes Dahuang (rhubarb), Houbu (Magnolia officinalis) and Zhishi (Immature Bitter Orange)<sup>[49]</sup>. MXD is a modified version of XD, with the addition of three components: Astragalus, Frankincense, and Myrrh on the basis of XD. Rhubarb, Astragalus, and Magnolia officinalis have immune protection effects and reduce the inflammatory stress response<sup>[50-61]</sup>. MXD may improve the recovery of GI function of patients with cholelithiasis in the perioperative period under ERAS. All of these results suggested the role of MXD in the improvement of the recovery of GI function, as evidenced by a patients’ early exhaust and defecation, early recovery of GI peristalsis, early feeding, and reduced incidence of nausea, vomiting, and bloating. Optimized treatment accelerates the postoperative recovery, which is consistent with the ERAS concept. In addition, regulation of the substance P level by MXD occurs in patients with cholelithiasis during the perioperative period, as substance P can increase the calcium transfer of Cajal interstitial cells in the small intestine to enhance the excitatory neuron response and promote GI peristalsis<sup>[27,62]</sup>. The serum level of substance P is significantly increased after the application of Betel nut, thereby promoting GI activity<sup>[63]</sup>. In our study, the serum level of substance P <sup>10</sup> in the MXD group was significantly higher than that in the control group on days 1 and 2 after surgery. Moreover, bowel sounds at 12 h after surgery, the time of both first flatus and first defecation was significantly correlated with substance P, suggesting that MXD may increase the secretion of substance P, thereby promoting the recovery of GI function. Furthermore, on the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery, <sup>2</sup> the levels of IL-6, CRP, and SAA in MXD group were lower than that in placebo control, but substance P level was higher, compared to control. In addition, there are significant correlations between indicators of GI function and inflammation. Therefore, it is further confirmed that postoperative



inflammatory response may lead to GI dysfunction. Treatment with MXD can reduce postoperative inflammatory stress response, and further promote the recovery of GI function. Because the specific mechanism related to the improvement of recovery of GI function is still not fully clear, further investigation is required. Since this study had some limitations, more indicators for detection and data analyses with large samples collected from multicenter studies are also needed and are ongoing from our group.

## **CONCLUSION**

Treatment with MXD can reduce the inflammatory response and improve GI function after surgery. Moreover, a close correlation between inflammatory response and GI function was found in our study, however, the pathophysiological relationship between them remains unclear. Furthermore, there is no serious adverse reactions in MXD treatment. Our observations provide insights into the possible role of inflammatory stress response in the pathogenesis of PGID and support the development of novel therapeutic strategies for the prevention and treatment of postoperative inflammatory stress response and PGID.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

In the perioperative period of biliary surgery, various factors can induce the release of a large number of inflammatory factors, leading to an imbalance in pro-inflammatory and anti-inflammatory responses and resulting in gastrointestinal (GI) dysfunction. It is crucial to reduce the inflammatory response and promote the recovery of GI function after biliary surgery, both of which are the basis and key for perioperative care and postoperative recovery.

### ***Research motivation***

Since lack of effective measures to reduce inflammatory response and promote the recovery of GI function after biliary surgery; therefore, it is necessary to develop novel interventions to reduce the stress response and accelerate postoperative recovery.

### ***Research objectives***

To better understand the effects of Modified Xiao-Cheng-Qi decoction (MXD) on the inflammatory response and GI function in perioperative of cholelithiasis, also their correlation, we conducted this study.

### ***Research methods***

This was a prospective randomized placebo-controlled trial, in which 162 patients who received biliary tract surgery, were randomly assigned to three groups: MXD group, XD group, and placebo-control group. The parameters included frequency of bowel sounds, time of first flatus and defecation, time of diet, and amount of activity after surgery. The serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), IL-10, serum amyloid A (SAA) protein, and substance P were measured.

### ***Research results***

Compared to the placebo-control, improvements in GI function were observed in the MXD groups, such as reduced incidence of nausea, vomiting, and bloating, and the earlier first exhaust time, first defecation time, and feeding time after surgery ( $P < 0.05$ ). On the 1<sup>st</sup> and 2<sup>nd</sup> d after surgery, serum levels of IL-6, CRP, and SAA in MXD group were lower than that in placebo control, but substance P level was higher, compared to the control ( $P < 0.05$ ).

### ***Research conclusions***

Treatment with MXD can relieve inflammatory response and improve GI function after surgery. Moreover, there are significant correlations between them.

### *Research perspectives*

The future research project will focus on the mechanism of MXD to reduce inflammatory reaction and improve GI function.

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