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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

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**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](https://www.baidu.com/Link?url=J7f8zZRjEBhrE069LEG21PPoSPqa3Yizn_6Of-Ild6_NOTAAJAzeDLaNCBEDzSaE_61ngmsglR7M9PvvS_G-y82aMfM3cXAXKoJ7euXXAOYF6B7B_1HaKCZhUsmisalw&wd=&eqid=f26620a70002a6a9000000045e8c8a1a) (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 1st and 2nd 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[1-4], leading to an imbalance in pro-inflammatory and anti-inflammatory responses and result in gastrointestinal (GI) dysfunction[5-7]. 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[8-11].ERAS protocols in biliary surgery have been shown to reduce the stress response and accelerate postoperative recovery[12-14]. 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[15-17]. 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: (1) Confirmed diagnosis of cholelithiasis, surgical indications; (2) Written informed consent for surgery; (3) Underwent elective laparoscopic choledocholithotomy and cholecystectomy or laparoscopic cholecystectomy; > 18 years and ≤ 75 years; (4) Had no severe cardiopulmonary complications and American Society of Anesthesiologists grade (ASA) I or II; and (5) Underwent primary biliary tract surgery. Exclusion criteria were: (1) 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; (2) Had undergone an emergency operation; (3) Had undergone reoperation of the biliary tract; (4) Had severe cardiopulmonary complications; or (5) 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 H2O; 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, remifentanil (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 mmgh, 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”[18] and “Nurse’s guide to common postoperative complications”[19]. Incision complications include surgical site infections, dehiscence, seromas, and hematomas[20]. Intra-abdominal infection is a common disease process after operation, which is associated with substantial morbidity and death[21]. Deep-vein thrombosisa is a condition in which a blood clot forms in a deep vein and causes a blockage[22]. Bile leakage originates from the cut surface of the liver, from injury of the bile ducts, or from anastomotic leakage after bilioenteric anastomosis[23]. 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[24]. 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[25]. 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”[26].

A comparison of the serum levels of C-reactive protein (CRP), [interleukin](https://www.baidu.com/Link?url=J7f8zZRjEBhrE069LEG21PPoSPqa3Yizn_6Of-Ild6_NOTAAJAzeDLaNCBEDzSaE_61ngmsglR7M9PvvS_G-y82aMfM3cXAXKoJ7euXXAOYF6B7B_1HaKCZhUsmisalw&wd=&eqid=f26620a70002a6a9000000045e8c8a1a)-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[27].

***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 physicalactivity 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%)[28,29]. 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 1st before surgery and 1st, 2nd d after surgery (*P* < 0.05). There was no significant difference among the three groups on the 3rd, 4th and 5th d after surgery (*P* > 0.05) (Table 7).

***Inflammatory indicators and substance P***

**IL-6:** On the 1st, 2nd, and 5th d after surgery, the serum concentrations of IL-6 in the three groups were higher than that on the 1st d before operation (*P* < 0.05). It is notable that on the 1st 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 2nd 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 1st d before surgery and 5th d after surgery (*P* > 0.05) (Table 8).

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

**CRP and SAA:** On the 1st and 2nd d after surgery, the serum concentrations of CRP and SAA in the three groups were higher than that on the 1st d before surgery (*P* < 0.05). It is notable that on the 5th 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 1st d before surgery (*P* < 0.05). On the 1st 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 2nd 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 1st d before surgery and 5th d after surgery (*P* > 0.05) (Table 8).

**Substance P:** On the 1st and 2nd d after surgery, the serum concentration of substance P in the MXD group was higher than that on the 1st d before surgery (*P* < 0.05). Our study also found that on the 1st 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 2nd 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 2nd d after surgery (r = -0.25, -0.22, -0.33; *P* ≤ 0.001, *P* ≤ 0.001, and *P* ≤ 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* ≤ 0.001, *P* = 0.01, respectively), While the occurring time of the first defecation showed its correlation with CRP and SAA levels on the 2nd d after surgery (r = 0.30, 0.24; *P* ≤ 0.001, *P* ≤ 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 2nd d after surgery (r = 0.27, 0.29; *P* ≤ 0.001, *P* ≤ 0.001, respectively). In addition, the level of substance P and SAA on the 2nd d after surgery showed a significant correlation (r = -0.24; *P* ≤ 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, -025; *P* ≤ 0.001, *P* ≤ 0.001, and *P* ≤ 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[10,11]. Moderate inflammatory response in the perioperative period is associated with the defense response and maintenance of homeostasis[30]. 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[31] and the imbalance between pro-inflammatory mediators and anti-inflammatory mediators eventually lead to systemic inflammatory response syndrome and GI dysfunction[32-35].

IL-6 is a main postoperative proinflammatory factor and a reliable predictor of systemic inflammatory response syndrome[36], which is also positively correlated with the severity of surgical trauma[37]. In the randomized controlled trials, Wang *et al*[38] and Chen *et al*[39] 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[40]. For example, Rahr *et al*[41] and Oldenburg *et al*[42] 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[43]. 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[44,45], so that both of them can be used as the main indicators for evaluating postoperative trauma, detecting septic shock and predicting organ failure[46]. Actually, Li *et al*[47] and Jung *et al*[48] 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 1st and 2nd 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)[49].MXD is a modified version of XD, with the addition of three components: Astragalus, Frankincense, and Myrrh on the basis of XD. Rhubarb[50-53], Astragalus[54-58], and Magnolia officinalis[59-61] have immune protection effects and reduce the inflammatory stress response. 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[27,62]. The serum level of substance P is significantly increased after the application of Betel nut, thereby promoting GI activity[63]. In our study, the serum level of substance P 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 1st and 2nd d after surgery, 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](https://www.baidu.com/Link?url=J7f8zZRjEBhrE069LEG21PPoSPqa3Yizn_6Of-Ild6_NOTAAJAzeDLaNCBEDzSaE_61ngmsglR7M9PvvS_G-y82aMfM3cXAXKoJ7euXXAOYF6B7B_1HaKCZhUsmisalw&wd=&eqid=f26620a70002a6a9000000045e8c8a1a)-6 (IL-6), [IL](https://www.baidu.com/Link?url=J7f8zZRjEBhrE069LEG21PPoSPqa3Yizn_6Of-Ild6_NOTAAJAzeDLaNCBEDzSaE_61ngmsglR7M9PvvS_G-y82aMfM3cXAXKoJ7euXXAOYF6B7B_1HaKCZhUsmisalw&wd=&eqid=f26620a70002a6a9000000045e8c8a1a)-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 1st and 2nd 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.

**REFERENCES**

1 **Hossain M**, Kubes P. Innate immune cells orchestrate the repair of sterile injury in the liver and beyond. *Eur J Immunol* 2019; **49**: 831-841 [PMID: 31001813 DOI: 10.1002/eji.201847485]

2 **Dobson GP**. Addressing the Global Burden of Trauma in Major Surgery. *Front Surg* 2015; **2**: 43 [PMID: 26389122 DOI: 10.3389/fsurg.2015.00043]

3 **O'Dwyer MJ**, Owen HC, Torrance HD. The perioperative immune response. *Curr Opin Crit Care* 2015; **21**: 336-342 [PMID: 26103142 DOI: 10.1097/MCC.0000000000000213]

4 **McDonald B**, Kubes P. Innate Immune Cell Trafficking and Function During Sterile Inflammation of the Liver. *Gastroenterology* 2016; **151**: 1087-1095 [PMID: 27725145 DOI: 10.1053/j.gastro.2016.09.048]

5 **Margraf A**, Ludwig N, Zarbock A, Rossaint J. Systemic Inflammatory Response Syndrome After Surgery: Mechanisms and Protection. *Anesth Analg* 2020; **131**: 1693-1707 [PMID: 33186158 DOI: 10.1213/ANE.0000000000005175]

6 **Alazawi W**, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and Immune Responses to Surgery and Their Clinical Impact. *Ann Surg* 2016; **264**: 73-80 [PMID: 27275778 DOI: 10.1097/SLA.0000000000001691]

7 **Alhayyan A**, McSorley S, Roxburgh C, Kearns R, Horgan P, McMillan D. The effect of anesthesia on the postoperative systemic inflammatory response in patients undergoing surgery: A systematic review and meta-analysis. *Surg Open Sci* 2020; **2**: 1-21 [PMID: 32754703 DOI: 10.1016/j.sopen.2019.06.001]

8 **Kehlet H**. Enhanced Recovery After Surgery (ERAS): good for now, but what about the future? *Can J Anaesth* 2015; **62**: 99-104 [PMID: 25391731 DOI: 10.1007/s12630-014-0261-3]

9 **Page AJ**, Ejaz A, Spolverato G, Zavadsky T, Grant MC, Galante DJ, Wick EC, Weiss M, Makary MA, Wu CL, Pawlik TM. Enhanced recovery after surgery protocols for open hepatectomy--physiology, immunomodulation, and implementation. *J Gastrointest Surg* 2015; **19**: 387-399 [PMID: 25472030 DOI: 10.1007/s11605-014-2712-0]

10 **Taurchini M**, Del Naja C, Tancredi A. Enhanced Recovery After Surgery: a patient centered process. *J Vis Surg* 2018; **4**: 40 [PMID: 29552522 DOI: 10.21037/jovs.2018.01.20]

11 **Carli F**. Physiologic considerations of Enhanced Recovery After Surgery (ERAS) programs: implications of the stress response. *Can J Anaesth* 2015; **62**: 110-119 [PMID: 25501695 DOI: 10.1007/s12630-014-0264-0]

12 **Kapritsou M**. Impact of the Enhanced Recovery Program after Hepato-Pancreato-Biliary Surgery. *Asia Pac J Oncol Nurs* 2019; **6**: 333-335 [PMID: 31572751 DOI: 10.4103/apjon.apjon\_15\_19]

13 **Ljungqvist O**. ERAS--enhanced recovery after surgery: moving evidence-based perioperative care to practice. *JPEN J Parenter Enteral Nutr* 2014; **38**: 559-566 [PMID: 24567343 DOI: 10.1177/0148607114523451]

14 **Peng H**, Zhang Q, Qian J, Ruan F, Mai H, Wang Z, Liu M, Wang Z, Chen H, Li J, Zhu B, Li C, Wang K, Zhou J. Electrolyte disorders are ERAS-associated in patients undergoing hepato-pancreato-biliary surgery. *Langenbecks Arch Surg* 2020; **405**: 603-611 [PMID: 32710380 DOI: 10.1007/s00423-020-01922-y]

15 **Lau CS**, Chamberlain RS. Enhanced Recovery After Surgery Programs Improve Patient Outcomes and Recovery: A Meta-analysis. *World J Surg* 2017; **41**: 899-913 [PMID: 27822725 DOI: 10.1007/s00268-016-3807-4]

16 **Gentile LF**, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg* 2012; **72**: 1491-1501 [PMID: 22695412 DOI: 10.1097/TA.0b013e318256e000]

17 **Chao A**, Chou WH, Chang CJ, Lin YJ, Fan SZ, Chao AS. The admission systemic inflammatory response syndrome predicts outcome in patients undergoing emergency surgery. *Asian J Surg* 2013; **36**: 99-103 [PMID: 23810158 DOI: 10.1016/j.asjsur.2013.01.001]

18 **Tazuma S**, Unno M, Igarashi Y, Inui K, Uchiyama K, Kai M, Tsuyuguchi T, Maguchi H, Mori T, Yamaguchi K, Ryozawa S, Nimura Y, Fujita N, Kubota K, Shoda J, Tabata M, Mine T, Sugano K, Watanabe M, Shimosegawa T. Evidence-based clinical practice guidelines for cholelithiasis 2016. *J Gastroenterol* 2017; **52**: 276-300 [PMID: 27942871 DOI: 10.1007/s00535-016-1289-7]

19 **Dennison RD**. Nurse's guide to common postoperative complications. *Nursing* 1997; **27**: 56-59 [PMID: 9397833 DOI: 10.1097/00152193-199711000-00027]

20 **Scalise A**, Calamita R, Tartaglione C, Pierangeli M, Bolletta E, Gioacchini M, Gesuita R, Di Benedetto G. Improving wound healing and preventing surgical site complications of closed surgical incisions: a possible role of Incisional Negative Pressure Wound Therapy. A systematic review of the literature. *Int Wound J* 2016; **13**: 1260-1281 [PMID: 26424609 DOI: 10.1111/iwj.12492]

21 **Mazuski JE**, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, Chang PK, O'Neill PJ, Mollen KP, Huston JM, Diaz JJ Jr, Prince JM. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. *Surg Infect (Larchmt)* 2017; **18**: 1-76 [PMID: 28085573 DOI: 10.1089/sur.2016.261]

22 **Wade R**, Sideris E, Paton F, Rice S, Palmer S, Fox D, Woolacott N, Spackman E. Graduated compression stockings for the prevention of deep-vein thrombosis in postoperative surgical patients: a systematic review and economic model with a value of information analysis. *Health Technol Assess* 2015; **19**: 1-220 [PMID: 26613365 DOI: 10.3310/hta19980]

23 **Koch M**, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, Fan ST, Yokoyama Y, Crawford M, Makuuchi M, Christophi C, Banting S, Brooke-Smith M, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Nimura Y, Figueras J, DeMatteo RP, Büchler MW, Weitz J. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 2011; **149**: 680-688 [PMID: 21316725 DOI: 10.1016/j.surg.2010.12.002]

24 **Metz A**, Hebbard G. Nausea and vomiting in adults--a diagnostic approach. *Aust Fam Physician* 2007; **36**: 688-692 [PMID: 17885699]

25 **Malagelada JR**, Accarino A, Azpiroz F. Bloating and Abdominal Distension: Old Misconceptions and Current Knowledge. *Am J Gastroenterol* 2017; **112**: 1221-1231 [PMID: 28508867 DOI: 10.1038/ajg.2017.129]

26 **Edwards IR**, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255-1259 [PMID: 11072960 DOI: 10.1016/S0140-6736(00)02799-9]

27 **Kim BJ**, Chang IY, Choi S, Jun JY, Jeon JH, Xu WX, Kwon YK, Ren D, So I. Involvement of Na(+)-leak channel in substance P-induced depolarization of pacemaking activity in interstitial cells of Cajal. *Cell Physiol Biochem* 2012; **29**: 501-510 [PMID: 22508057 DOI: 10.1159/000338504]

28 **Holtmann GJ**, Talley NJ. Inconsistent symptom clusters for functional gastrointestinal disorders in Asia: is Rome burning? *Gut* 2018; **67**: 1911-1915 [PMID: 29921653 DOI: 10.1136/gutjnl-2017-314775]

29 **Hou ZK**, Hu W, Liu FB, Xiao JX, Lyu ZP. [Inspirations of Rome Ⅳ on clinical evaluation of traditional Chinese medicine for functional gastrointestinal disease]. *Zhongguo Zhong Yao Za Zhi* 2018; **43**: 2168-2176 [PMID: 29933688 DOI: 10.19540/j.cnki.cjcmm.20180307.007]

30 **Shankar Hari M**, Summers C. Major surgery and the immune system: from pathophysiology to treatment. *Curr Opin Crit Care* 2018; **24**: 588-593 [PMID: 30299310 DOI: 10.1097/MCC.0000000000000561]

31 **Kimura F**, Shimizu H, Yoshidome H, Ohtsuka M, Miyazaki M. Immunosuppression following surgical and traumatic injury. *Surg Today* 2010; **40**: 793-808 [PMID: 20740341 DOI: 10.1007/s00595-010-4323-z]

32 **Binkowska AM**, Michalak G, Słotwiński R. Current views on the mechanisms of immune responses to trauma and infection. *Cent Eur J Immunol* 2015; **40**: 206-216 [PMID: 26557036 DOI: 10.5114/ceji.2015.52835]

33 **Hill TL**. Gastrointestinal Tract Dysfunction With Critical Illness: Clinical Assessment and Management. *Top Companion Anim Med* 2019; **35**: 47-52 [PMID: 31122688 DOI: 10.1053/j.tcam.2019.04.002]

34 **Li H**, He T, Xu Q, Li Z, Liu Y, Li F, Yang BF, Liu CZ. Acupuncture and regulation of gastrointestinal function. *World J Gastroenterol* 2015; **21**: 8304-8313 [PMID: 26217082 DOI: 10.3748/wjg.v21.i27.8304]

35 **Reintam Blaser A**, Preiser JC, Fruhwald S, Wilmer A, Wernerman J, Benstoem C, Casaer MP, Starkopf J, van Zanten A, Rooyackers O, Jakob SM, Loudet CI, Bear DE, Elke G, Kott M, Lautenschläger I, Schäper J, Gunst J, Stoppe C, Nobile L, Fuhrmann V, Berger MM, Oudemans-van Straaten HM, Arabi YM, Deane AM; Working Group on Gastrointestinal Function within the Section of Metabolism, Endocrinology and Nutrition (MEN Section) of ESICM. Gastrointestinal dysfunction in the critically ill: a systematic scoping review and research agenda proposed by the Section of Metabolism, Endocrinology and Nutrition of the European Society of Intensive Care Medicine. *Crit Care* 2020; **24**: 224 [PMID: 32414423 DOI: 10.1186/s13054-020-02889-4]

36 **Fink-Neuboeck N**, Lindenmann J, Bajric S, Maier A, Riedl R, Weinberg AM, Smolle-Juettner FM. Clinical impact of interleukin 6 as a predictive biomarker in the early diagnosis of postoperative systemic inflammatory response syndrome after major thoracic surgery: A prospective clinical trial. *Surgery* 2016; **160**: 443-453 [PMID: 27206334 DOI: 10.1016/j.surg.2016.04.004]

37 **Jawa RS**, Anillo S, Huntoon K, Baumann H, Kulaylat M. Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. *J Intensive Care Med* 2011; **26**: 73-87 [PMID: 21464062 DOI: 10.1177/0885066610384188]

38 **Wang G**, Jiang Z, Zhao K, Li G, Liu F, Pan H, Li J. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012; **16**: 1379-1388 [PMID: 22585532 DOI: 10.1007/s11605-012-1880-z]

39 **Chen L**, Sun L, Lang Y, Wu J, Yao L, Ning J, Zhang J, Xu S. Fast-track surgery improves postoperative clinical recovery and cellular and humoral immunity after esophagectomy for esophageal cancer. *BMC Cancer* 2016; **16**: 449 [PMID: 27401305 DOI: 10.1186/s12885-016-2506-8]

40 **Bedke T**, Muscate F, Soukou S, Gagliani N, Huber S. Title: IL-10-producing T cells and their dual functions. *Semin Immunol* 2019; **44**: 101335 [PMID: 31734129 DOI: 10.1016/j.smim.2019.101335]

41 **Rahr HB**, Bendix J, Ahlburg P, Gjedsted J, Funch-Jensen P, Tønnesen E. Coagulation, inflammatory, and stress responses in a randomized comparison of open and laparoscopic repair of recurrent inguinal hernia. *Surg Endosc* 2006; **20**: 468-472 [PMID: 16437269 DOI: 10.1007/s00464-005-0305-4]

42 **Oldenburg HS**, Siroen MP, Boelens PG, Sluijter BJ, Pruitt JH, Naseri AH, Rauwerda JA, Meijer S, Cuesta MA, van Leeuwen PA, Moldawer LL. Aortic aneurysm repair is associated with a lower inflammatory response compared with surgery for inflammatory bowel disease. *Eur Surg Res* 2004; **36**: 266-273 [PMID: 15359089 DOI: 10.1159/000079911]

43 **Strnad P**, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 55-66 [PMID: 27924081 DOI: 10.1038/nrgastro.2016.168]

44 **Pathak A**, Agrawal A. Evolution of C-Reactive Protein. *Front Immunol* 2019; **10**: 943 [PMID: 31114584 DOI: 10.3389/fimmu.2019.00943]

45 **Sun L**, Ye RD. Serum amyloid A1: Structure, function and gene polymorphism. *Gene* 2016; **583**: 48-57 [PMID: 26945629 DOI: 10.1016/j.gene.2016.02.044]

46 **Wierdak M**, Pisarska M, Kuśnierz-Cabala B, Witowski J, Major P, Ceranowicz P, Budzyński A, Pędziwiatr M. Serum Amyloid A as an Early Marker of Infectious Complications after Laparoscopic Surgery for Colorectal Cancer. *Surg Infect (Larchmt)* 2018; **19**: 622-628 [PMID: 30004836 DOI: 10.1089/sur.2018.105]

47 **Li L**, Chen J, Liu Z, Li Q, Shi Y. Enhanced recovery program versus traditional care after hepatectomy: A meta-analysis. *Medicine (Baltimore)* 2017; **96**: e8052 [PMID: 28930840 DOI: 10.1097/MD.0000000000008052]

48 **Jung IK**, Kim MC, Kim KH, Kwak JY, Jung GJ, Kim HH. Cellular and peritoneal immune response after radical laparoscopy-assisted and open gastrectomy for gastric cancer. *J Surg Oncol* 2008; **98**: 54-59 [PMID: 18521842 DOI: 10.1002/jso.21075]

49 **Fan MX**, Wang HJ, Li XM, Li PY, Bian BL. [Studies on chemical constituents and volatile oil of Xiaochengqi decoction]. *Zhongguo Zhong Yao Za Zhi* 2008; **33**: 1027-1031 [PMID: 18652350]

50 **Chen X**, Yang K, Jing G, Yang J, Li K. Meta-Analysis of Efficacy of Rhubarb Combined With Early Enteral Nutrition for the Treatment of Severe Acute Pancreatitis. *JPEN J Parenter Enteral Nutr* 2020; **44**: 1066-1078 [PMID: 32187391 DOI: 10.1002/jpen.1789]

51 **Cao YJ**, Pu ZJ, Tang YP, Shen J, Chen YY, Kang A, Zhou GS, Duan JA. Advances in bio-active constituents, pharmacology and clinical applications of rhubarb. *Chin Med* 2017; **12**: 36 [PMID: 29299052 DOI: 10.1186/s13020-017-0158-5]

52 **Liu X**, Wu J, Tian R, Su S, Deng S, Meng X. Targeting foam cell formation and macrophage polarization in atherosclerosis: The Therapeutic potential of rhubarb. *Biomed Pharmacother* 2020; **129**: 110433 [PMID: 32768936 DOI: 10.1016/j.biopha.2020.110433]

53 **Cai J**, Xuan ZR, Wei YP, Yang HB, Wang H. [Effects of perioperative administration of Rhubarb on acute inflammatory response in patients with gastric cancer]. *Zhong Xi Yi Jie He Xue Bao* 2005; **3**: 195-198 [PMID: 15885167 DOI: 10.3736/jcim20050309]

54 **Ghasemian-Yadegari J**, Hamedeyazdan S, Nazemiyeh H, Fathiazad F. Evaluation of Phytochemical, Antioxidant and Antibacterial Activity on Astragalus Chrysostachys Boiss. Roots. *Iran J Pharm Res* 2019; **18**: 1902-1911 [PMID: 32184856 DOI: 10.22037/ijpr.2019.1100855]

55 **Li W**, Sun YN, Yan XT, Yang SY, Kim S, Lee YM, Koh YS, Kim YH. Flavonoids from Astragalus membranaceus and their inhibitory effects on LPS-stimulated pro-inflammatory cytokine production in bone marrow-derived dendritic cells. *Arch Pharm Res* 2014; **37**: 186-192 [PMID: 23771500 DOI: 10.1007/s12272-013-0174-7]

56 **Adesso S**, Russo R, Quaroni A, Autore G, Marzocco S. Astragalus membranaceus Extract Attenuates Inflammation and Oxidative Stress in Intestinal Epithelial Cells via NF-κB Activation and Nrf2 Response. *Int J Mol Sci* 2018; **19** [PMID: 29534459 DOI: 10.3390/ijms19030800]

57 **Clement-Kruzel S**, Hwang SA, Kruzel MC, Dasgupta A, Actor JK. Immune modulation of macrophage pro-inflammatory response by goldenseal and Astragalus extracts. *J Med Food* 2008; **11**: 493-498 [PMID: 18800897 DOI: 10.1089/jmf.2008.0044]

58 **Wang X**, Li Y, Yang X, Yao J. Astragalus polysaccharide reduces inflammatory response by decreasing permeability of LPS-infected Caco2 cells. *Int J Biol Macromol* 2013; **61**: 347-352 [PMID: 23916649 DOI: 10.1016/j.ijbiomac.2013.07.013]

59 **Poivre M**, Duez P. Biological activity and toxicity of the Chinese herb Magnolia officinalis Rehder & E. Wilson (Houpo) and its constituents. *J Zhejiang Univ Sci B* 2017; **18**: 194-214 [PMID: 28271656 DOI: 10.1631/jzus.B1600299]

60 **Shih HC**, Kuo PC, Wu SJ, Hwang TL, Hung HY, Shen DY, Shieh PC, Liao YR, Lee EJ, Gu Q, Lee KH, Wu TS. Anti-inflammatory neolignans from the roots of Magnolia officinalis. *Bioorg Med Chem* 2016; **24**: 1439-1445 [PMID: 26928286 DOI: 10.1016/j.bmc.2016.01.049]

61 **Li CY**, Chao LK, Wang SC, Chang HZ, Tsai ML, Fang SH, Liao PC, Ho CL, Chen ST, Cheng WC, Chiang CS, Kuo YH, Hua KF, Hsu IC. Honokiol inhibits LPS-induced maturation and inflammatory response of human monocyte-derived dendritic cells. *J Cell Physiol* 2011; **226**: 2338-2349 [PMID: 21660957 DOI: 10.1002/jcp.22576]

62 **Baker SA**, Drumm BT, Skowronek KE, Rembetski BE, Peri LE, Hennig GW, Perrino BA, Sanders KM. Excitatory Neuronal Responses of Ca(2+) Transients in Interstitial Cells of Cajal in the Small Intestine. *eNeuro* 2018; **5** [PMID: 29632869 DOI: 10.1523/ENEURO.0080-18.2018]

63 **Zhang S**, Yang P, Li X, Wang X, Song J, Peng W, Wu C. Comparative Researches of Semen Arecae and Charred Semen Arecae on Gastrointestinal Motility, Motilin, Substance P, and CCK in Chronically Stressed Rats. *Evid Based Complement Alternat Med* 2017; **2017**: 1273561 [PMID: 29375638 DOI: 10.1155/2017/1273561]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of Binzhou Medical University Hospital [No. Ethical research (2017-026-01)].

**Clinical trial registration statement:** This study is registered at ClinicalTrials.gov. The registration identification number is ChiCTR2000033125.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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**Data sharing statement:** Technical appendix, statistical code, and dataset are available from the corresponding author at chenqiangpu@bzmc.edu.cn. Participants gave informed consent for data sharing.

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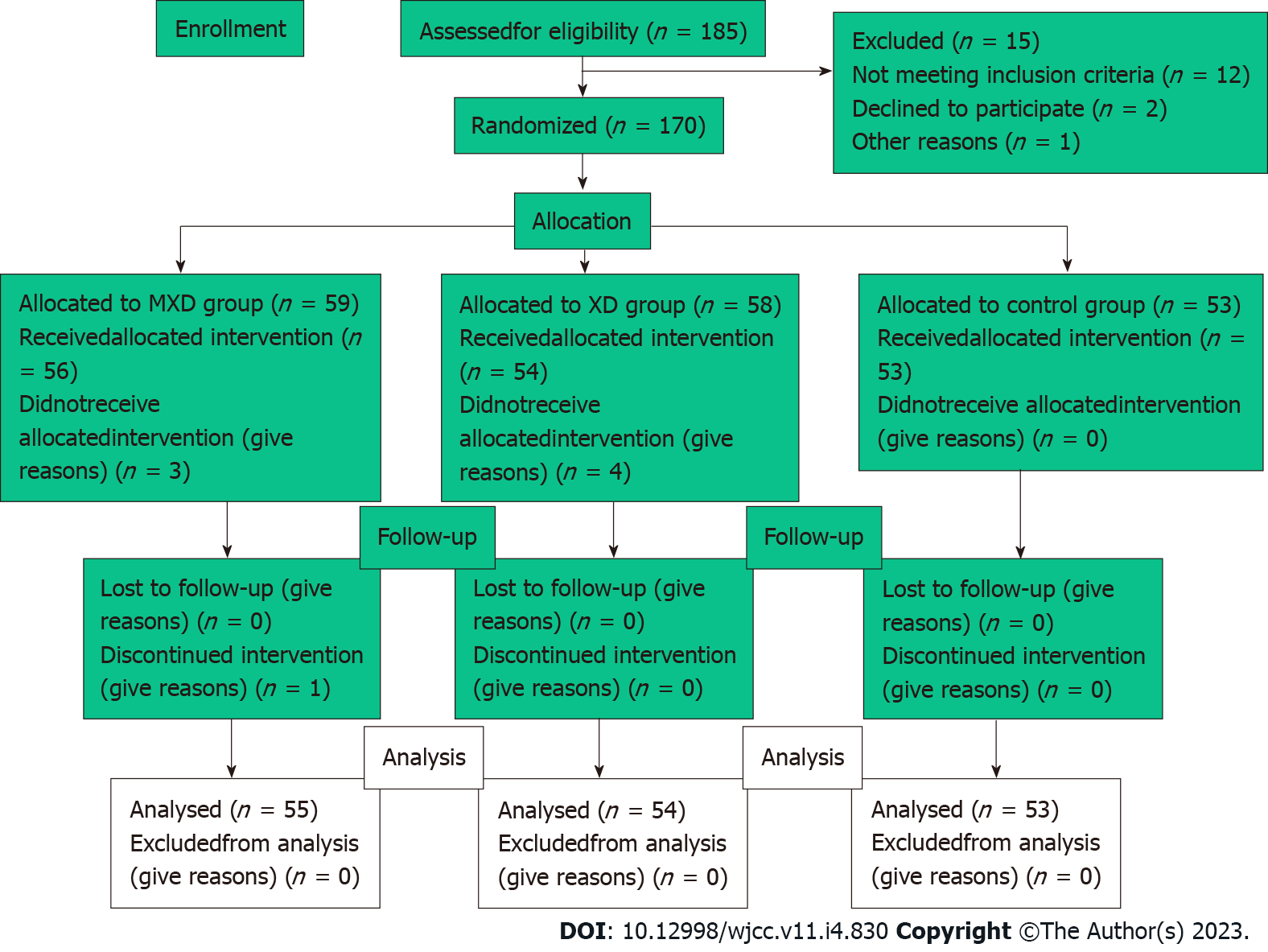
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**Figure Legends**



**Figure 1 Patients’ flowchart.** XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 1 All ingredients of the different treatment group**

|  |  |
| --- | --- |
| **Group** | **Ingredient** |
| Control | Warm boiled water |
| XD | Dahuang (Rhubarb) 6 g, Houbu (Magnolia officinalis) 6 g and Zhishi (Immature Bitter Orange) 12 g |
| MXD | Dahuang (Rhubarb) 6 g, Houbu (Magnolia officinalis) 6 g, Zhishi (Immature Bitter Orange) 12 g, Huangqi (Astragalus) 20 g, Ruxiang (Frankincense) 6 g and Moyao (Myrrh) 6 g |

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 2 Basic characteristics of the participants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics/group** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| Age (yr) | 57.19 ± 13.19 | 55.44 ± 15.75 | 54.53 ± 15.36 | 0.640 |
| Sex |  |  |  | 0.782 |
| Male | 23 (43.4%) | 26 (48.1%) | 24 (43.6%) |  |
| Female | 30 (56.6%) | 28 (51.9%) | 31 (56.4%) |  |
| BMI (kg/m2) | 23.84 ± 1.85 | 23.78 ± 2.01 | 24.06 ± 1.64 | 0.701 |
| Concomitant disease |  |  |  | 0.917 |
| Yes | 30 (56.6%) | 28 (51.9%) | 29 (52.7%) |  |
| No | 23 (43.4%) | 26 (48.1%) | 26 (47.3%) |  |
| Operation mode |  |  |  | 0.997 |
| Laparoscopic cholecystectomy | 45 (84.9%) | 46 (85.2%) | 47 (85.5%) |  |
| Laparoscopic cholecystectomy and choledocholithotomy | 8 (15.1%) | 8 (14.85%) | 8 (14.5%) |  |
| Operation time (min) | 176.70 ± 47.02 | 178.89 ± 47.13 | 173.09 ± 49.36 | 0.816 |
| Intraoperative blood loss (mL) | 37.36 ± 22.80 | 37.04 ± 19.97 | 36.36 ± 19.94 | 0.969 |

XD: Xiao-Cheng-Qi decoction; MX: Modified Xiao-Cheng-Qi decoction; BMI: Body mass index.

**Table 3 Recovery of gastrointestinal function after biliary surgery**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| Bowel sounds (times/min) |  |  |  |  |
| 2 h before surgery | 4.66 ± 0.68 | 4.39 ± 0.86 | 4.42 ± 0.79 | 0.144 |
| 0 h after surgery | 0.02 ± 0.141 | 0.06 ± 0.231 | 0.15 ± 0.361,2 | 0.035 |
| 6 h after surgery | 2.21 ± 1.321 | 3.11 ± 1.571,2 | 3.24 ± 1.621,2 | 0.001 |
| 12 h after surgery | 3.77 ± 1.661 | 6.74 ± 1.991,2 | 7.65 ± 2.151,2,3 | 0.000 |
| 24 h after surgery | 3.95 ± 1.141 | 4.85 ± 1.391,2 | 5.18 ± 1.531,2 | 0.000 |
| Time of first flatus (h) | 24.00 ± 11.03 | 19.70 ± 10.212 | 17.40 ± 5.312 | 0.003 |
| Time of first defecation (h) | 55.75 ± 26.95 | 36.91 ± 15.202 | 34.42 ± 12.92 | 0.000 |

1*P* < 0.05 *vs* the same group 2 h before surgery.

2*P* < 0.05 *vs* the control group.

3*P* < 0.05 *vs* Xiao-Cheng-Qi decoction.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 4 Diet after biliary surgery**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| Postoperative drinking time (h) | 11.11 ± 7.26 | 8.88 ± 3.931 | 7.21 ± 3.201 | 0.076 |
| Postoperative liquid diet time (h) | 15.72 ± 8.98 | 12.74 ± 5.471 | 10.35 ± 4.241 | 0.049 |
| Postoperative semi-liquid diet time (h) | 27.92 ± 15.16 | 22.53 ± 9.331 | 17.98 ± 6.831,2 | 0.028 |
| Postoperative normal diet time (h) | 100.94 ± 39.04 | 94.80 ± 35.86 | 81.69 ± 29.07 | 0.333 |

1*P* < 0.05 *vs* the control group.

2*P* < 0.05 *vs* Xiao-Cheng-Qi decoction.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 5 Physical activity after biliary surgery**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Activity indicators** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| Activity time (min) |  |  |  |  |
| 1 d after surgery | 27.06 ± 8.29 | 28.50 ± 8.95 | 33.76 ± 12.411,2 | 0.107 |
| 2 d after surgery | 41.73 ± 11.59 | 48.07 ± 14.571 | 57.02 ± 19.911,2 | 0.157 |
| 3 d after surgery | 50.94 ± 12.00 | 61.91 ± 21.731 | 63.64 ± 19.631 | 0.201 |
| 4 d after surgery | 59.24 ± 12.81 | 68.75 ± 19.54 | 78.08 ± 35.141 | 0.130 |
| 5 d after surgery | 77.40 ± 21.77 | 85.17 ± 27.81 | 88.80 ± 22.32 | 0.481 |
| Activity distance (m) |  |  |  |  |
| 1 d after surgery | 256.70 ± 94.97 | 284.57 ± 80.77 | 344.35 ± 134.011,2 | 0.127 |
| 2 d after surgery | 397.19 ± 123.24 | 480.70 ± 163.851 | 630.60 ± 177.831,2 | 0.050 |
| 3 d after surgery | 505.19 ± 151.09 | 571.75 ± 177.87 | 730.21 ± 200.951,2 | 0.013 |
| 4 d after surgery | 651.82 ± 181.59 | 742.75 ± 195.40 | 782.69 ± 159.86 | 0.219 |
| 5 d after surgery | 788.27 ± 236.58 | 792.50 ± 195.48 | 937.10 ± 145.73 | 0.162 |

1*P* < 0.05 *vs* the control group.

2*P* < 0.05 *vs* Xiao-Cheng-Qi decoction.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 6 Incidence of complications after biliary surgery**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| Incision complications | 2 (3.77%) | 1 (1.85%) | 1 (1.82%) | 0.761 |
| Intra-abdominal infection | 1 (1.89%) | 0 (0%) | 0 (0%) | 0.761 |
| Deep-vein thrombosis | 0 (0%) | 0 (0%) | 0 (0%) | 1.000 |
| Bile leakage | 1 (1.89%) | 1 (1.85%) | 0 (0%) | 0.599 |
| Nausea and vomiting | 12 (22.64%) | 3 (5.56%)1 | 2 (3.64%)1 | 0.001 |
| Bloating | 11 (20.75%) | 4 (7.41%)1 | 3 (5.45%)1 | 0.009 |

1*P* < 0.05 *vs* the control group.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 7** **Incidence of functional diarrhea in perioperative period**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| 1d before surgery | 2 (3.77%) | 14 (25.93%)1 | 6 (10.91%)1,2 | 0.003 |
| 1d after surgery | 1 (1.89%) | 9 (16.67%)1 | 6 (10.91%)1 | 0.035 |
| 2 d after surgery | 0 (0%) | 8 (14.81%)1 | 5 (9.09%)1 | 0.017 |
| 3 d after surgery | 2 (3.77%) | 4 (7.41%) | 2 (3.64%) | 0.595 |
| 4 d after surgery | 1 (1.89%) | 2 (3.70%) | 1 (1.82%) | 0.777 |
| 5 d after surgery | 2 (3.77%) | 1 (1.85%) | 2 (3.64%) | 0.816 |

1*P* < 0.05 *vs* the control group.

2*P* < 0.05 *vs* Xiao-Cheng-Qi decoction.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction.

**Table 8 Levels of the indicators for acute inflammatory stress response and substance P in the perioperative period of biliary tract surgery**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicators** | **Control (*n* = 53)** | **XD (*n* = 54)** | **MXD (*n* = 55)** | ***P* value** |
| IL-6 (pg/mL) |  |  |  |  |
| 1 d before surgery | 4.89 ± 1.24 | 4.43 ± 1.46 | 4.26 ± 2.62 | 0.203 |
| 1 d after surgery | 17.42 ± 6.671 | 10.63 ± 9.991,2 | 9.08 ± 8.631,2 | 0.000 |
| 2 d after surgery | 11.09 ± 3.571 | 9.80 ± 6.511 | 6.13 ± 3.601,2,3 | 0.000 |
| 5 d after surgery | 8.49 ± 2.311 | 7.22 ± 2.171 | 7.22 ± 3.391 | 0.487 |
| IL-10 (pg/mL) |  |  |  |  |
| 1 d before surgery | 1.29 ± 0.50 | 1.25 ± 0.46 | 1.24 ± 0.23 | 0.798 |
| 1 d after surgery | 1.27 ± 0.49 | 1.20 ± 0.61 | 1.21 ± 0.50 | 0.761 |
| 2 d after surgery | 1.21 ± 0.51 | 1.23 ± 0.50 | 1.19 ± 0.37 | 0.942 |
| 5 d after surgery | 1.33 ± 0.55 | 1.45 ± 0.53 | 1.39 ± 0.42 | 0.865 |
| CRP (ng/mL) |  |  |  |  |
| 1 d before surgery | 6.19 ± 1.77 | 5.69 ± 2.40 | 5.59 ± 1.87 | 0.273 |
| 1 d after surgery | 16.85 ± 7.731 | 10.84 ± 8.381,2 | 8.02 ± 3.441,2,3 | 0.000 |
| 2 d after surgery | 17.90 ± 17.361 | 14.41 ± 11.361 | 8.83 ± 2.841,2,3 | 0.001 |
| 5 d after surgery | 10.33 ± 3.111 | 10.49 ± 1.45 | 8.52 ± 2.68 | 0.170 |
| SAA (ng/mL) |  |  |  |  |
| 1 d before surgery | 426.21 ± 48.96 | 415.64 ± 40.60 | 411.00 ± 47.39 | 0.214 |
| 1 d after surgery | 9492.64 ± 1738.161 | 7807.52 ± 936.931,2 | 6953.98 ± 1228.381,2,3 | 0.000 |
| 2 d after surgery | 14792.13 ± 6501.471 | 10573.74 ± 4074.711,2 | 9341.03 ± 1888.411,2 | 0.000 |
| 5 d after surgery | 7817.09 ± 550.521 | 7396.66 ± 611.021 | 6911.41 ± 1464.141 | 0.132 |
| Substance P (pg/mL) |  |  |  |  |
| 1 d before surgery | 40.73 ± 21.53 | 35.61 ± 19.79 | 36.14 ± 31.12 | 0.501 |
| 1 d after surgery | 33.60 ± 16.051 | 37.30 ± 16.07 | 49.25 ± 41.491,2,3 | 0.009 |
| 2 d after surgery | 28.23 ± 11.121 | 45.58 ± 24.071,2 | 51.73 ± 26.871,2 | 0.000 |
| 5 d after surgery | 28.29 ± 11.90 | 27.55 ± 23.99 | 35.48 ± 23.70 | 0.653 |

1*P* < 0.05 *vs* the same group before surgery.

2*P* < 0.05 *vs* the control group.

3*P* < 0.05 *vs* Xiao-Cheng-Qi decoction.

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction; IL: Interleukin; CRP: C-reactive protein; SAA: Serum amyloid A.

**Table 9 Spearman correlation between indicators of gastrointestinal function and inflammation on the second day after surgery (r, p)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | **IL-6** | **IL-10** | **CRP** | **SAA** | **Substance P** |
| Bowel sounds at 12 h after surgery | (0.25, ≤ 0.001) | (-0.03, 0.74) | (-0.22, ≤ 0.001) | (-0.33, ≤ 0.001) | (0.31, ≤ 0.001) |
| Time of first flatus | (0.20, 0.01) | (0.05, 0.55) | (0.35, ≤ 0.001) | (0.16, 0.04) | (-0.23, ≤ 0.001) |
| Time of first defecation | (0.14, 0.07) | (0.04, 0.59) | (0.30, ≤ 0.001) | (0.24, ≤ 0.001) | (-0.25, ≤ 0.001) |
| Postoperative liquid diet time | (0.19, 0.01) | (-0.02, 0.81) | (0.27, ≤ 0.001) | (0.08, 0.33) | (-0.10, 0.23) |
| Postoperative semi-liquid diet time | (0.09, 0.25) | (-0.00, 0.98) | (0.29, ≤ 0.001) | (0.11, 0.15) | (-0.15, 0.06) |
| Substance P | (-0.20, 0.01) | (-0.15, 0.06) | (-0.15, 0.05) | (-0.24, ≤ 0.001) | (1.00, ≤ 0.001) |

XD: Xiao-Cheng-Qi decoction; MXD: Modified Xiao-Cheng-Qi decoction; IL: Interleukin; CRP: C-reactive protein; SAA: Serum amyloid A.



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