Dear Dr. Ma,

Thank you very much for sending the decision letter to let us know the reviewers' comments to our manuscript entitled "Inflammatory response and gastrointestinal function in perioperative of cholelithiasis with effects of Modified Xiao- Cheng-Qi decoction (a new remedy with traditional Chinese medicine): A Randomized Placebo-Controlled Trial" (ID: 80535). Those comments are valuable and helpful for us to revise our manuscript, which not only improve the quality of our paper, but also promote our capability for scientific research. We have read reviewers' comments carefully, accordingly making a point-by-point response (see below) to address their concerns and criticisms. Furthermore, our manuscript has been revised according to those comments. The changes in the revised manuscript are marked in red.

We hope our revised manuscript can meet the requirements of your journal and be accepted for publication.

Yours sincerely,

Qiangpu Chen

Corresponding author

We really appreciate Editors/Reviewers' comments and suggestions.

A point-by-point response to the reviewer's comments:

Reviewer #1:
1.In the Methods, please state about the blinding status.
Response: Thank you for your constructive comments. As per your suggestion, we have added the following sentences to the Methods: "An investigator who was unaffiliated with the trial created the randomization list. This process was performed using SAS 9.4 software to generate a random sequence. The participants were randomly allocated at a 1:1:1 ratio to three groups. Thus, our study was a prospective randomized, double-blind and placebo-controlled trial." **(line 133-135, 154-157)**

2.Please state clearly how you assessed the study outcomes (e.g., bowel sounds, time of first defecation, labs, etc.)
Response: We appreciate your thoughtful comments and suggestion. Accordingly, we have revised this part by adding sentences to describe the evaluation methods and standards of the outcome indicators in detail. (**lines 242–280**)

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 abdomi- nal 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-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].

3. Sample size calculation should be mentioned in detail.

Response: As per the reviewer's suggestion, we have modified the sentences in the Methods to explain how to do sample size calculation. (**lines 133-142**)

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.

4. Please describe how the herbal intervention was prepared and used in more detail.

Response: Thank you very much for your constructive comments. We made a detailed explanation of the procedure of the preparation and use of the herbal intervention in the revised manuscript. (**lines 157–169**)

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); XD (Dahuang [rhubarb] 6 g, Houbu [Magnolia officinalis] 6 g, Zhishi [Immature Bitter Orange] 12 g); 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.

5. What were you limitations?

Response: To discuss the limitation of our study, we have discussed the limitations of this trial in more detail in the discussion section. In addition, we have described the inclusion and exclusion criteria used in this study in more detail. The stratification of this study is also introduced. (**lines 470-474, 171–183, 137–138**)

Because the specific mechanism related to the improvement of recovery of gastrointestinal 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.

2.2 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.

Participants were stratified according to the presence or absence of common bile duct stones.

6. Figure 1 is a CONSORT flow-diagram. Please cite it in your text.
Response: As per your suggestion, correction has been made by adding a sentence as follows in the revised manuscript. "A flow diagram of the patient enrollment and study phase schedule is shown in Figure 1." (**lines 148–149**)

7. Table 1: Please mention the p-values.
Response: Actually, the title of Table 1 was labeled not clearly, which may lead to reviewers' misunderstanding. Table 1 shows all ingredients of the different treatment group. In addition, thanks to the reviewer's reminder, we have added the p-value to Tables 2 to 9. (**lines 772–874**)

Reviewer #2:
1.The article does not explain how the authors randomly group the subjects.
Response: As the reviewer mentioned, we did not explain how to randomly assign a different group in the previous version of the manuscript. We have made corrections according to the reviewer's comments. (**lines 154–157**)

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.

2.The design of the tables is too simple, specific P values should be supplemented.
Response: Thank you for your constructive comments. Accordingly, the p-value has been added to Tables 2 to 8. (**lines 792–874**)

3.As an uncommon indicator, substance P is supposed to be briefly introduced in the previous part of the article.
Response: As you mentioned, substance P is an uncommon indicator. Accordingly, we have briefly introduced it in the part of outcome measures. **(lines 277–280)**

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[21].

4.The evaluation methods and standards of outcome indicators should be detailed in the methods part.

Response: It is true that we did not clearly explain how to evaluate the outcome indicators in the previous version of this article. As per your suggestion, the evaluation methods and standards of outcome indicators have been re-written in more detail. (**lines 242–280**)

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.

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5.Some indicators have significant difference between groups before the surgery, such as physical activity, incidence of physical diarrhea, does this mean that the baseline is different between the groups?

Response: The notes in Table 5 and Table 7 is not very clear, which may cause reviewer's misunderstanding about the difference of some indicators between groups. Here, we would clarify the purpose of Table 5 and Table 7. Table 5 shows the physical activity after biliary surgery. However, the physical activity before biliary surgery was not included. Table 7 shows the adverse reactions of the investigational remedy, such as functional diarrhea, which occurred in the three groups of patients who began to take the investigational remedy before surgery. Nevertheless, there were no significant differences in age, sex, body mass index (BMI), concomitant disease, surgery type, operation time, or intraoperative blood loss among those three groups ($P>0.05$), suggesting that the overall baseline parameters between groups are similar in our study. **(lines 295-299, 315–321, 333–338, 826–829, 844–847)**

Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA).

Response: According to your requirements for publication, we changed the title to "Improvement of inflammatory response and gastrointestinal function in perioperative of cholelithiasis by Modified Xiao-Cheng-Qi decoction" (15 words), which makes the title more concise. Thank you for recommending the Reference Citation Analysis, a new tool for publication.