

Dear editors,

We have revised the paper as your requested. The details are as follows:

Words in blue color are your requests. And words in black color are my answers.

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors comment on study that examined the effect of alternative medicine in treatment of heart burn. It discuss the positives and negatives of the study. However authors should follow more or less the flow of letter to editor. It needs to summarize the status of problem, the actual study design, findings followed by discussing the strength and limitation of the study. By reading this part: me as a reader will not need to go back and read the study. This part will need to be redone for the letter to be accepted in my opinion. I read the letter and was not able to understand what is the actual study discussed was in sufficient detail Then authors need to reflect on the study. Their comments and understanding of the study then how authors think the findings can be applied and discuss future directions.

A: *The paper was rechecked by a native speaker in order to improve language quality.*

Thank you for the recommendation.

We rewrite the main text. (added words are in red color)

Old version

We read with interest a clinical study by Li et al.^[1]. The researchers performed a prospective, double-blinded, and double-simulation study on the efficacy of Modified Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GERD) and its effect on esophageal motility.

GERD has a high prevalence worldwide with limited therapeutic options, and its incidence is increasing annually. Traditional Chinese Medicine believes that the herb Chaihu could regulate Qi-flow to harmonize digestive disorders. The formula for Xiaochaihu Decoction, which has demonstrated therapeutic effects for nausea, poor appetite, epigastric distension, etc., has been applied for treating GERD for thousands of years in Asian countries. However, high-level evidence-based medical research is still lacking. Li et al. conducted a well-designed clinical study evaluating the efficacy of MXD for GERD and its effect on esophageal motility. Although the number of cases at secondary endpoints was low, the study results suggest that MXD could have therapeutic effects in GERD. High-quality randomized controlled trials require a larger number of patients.

However, it is important to record the side effects in this clinical study. Proton pump inhibitors (PPIs), a standard treatment strategy for GERD, increase the risk of infections, osteoporosis, hepatic failure, pancreatitis, jaundice, and gynecomastia^[2-4]. MXD may also cause additional side effects. Li et al. summarized the increased risk of overdose-induced acute or accumulation-related chronic hepatotoxicity of Bupleurum^[5]. Furthermore, Lee et al. reported a higher risk of liver diseases in their clinical observations in patients who used MXD or a high dose of Bupleurum^[6]. Meanwhile, Itoh et al. reported that long-term oral administration of MXD causes cholestatic liver injury, interstitial pneumonia, and even death^[7]. Therefore, medical safety evaluation tests, such as liver and kidney function indices, should be assessed. Rescue medication or treatment should also be considered. The authors mainly focused on the efficiency of MXD therapy for a short duration. Further studies are needed to examine the effects of prolonged MXD therapy on GERD rehabilitation.

New version

We read with interest a clinical study by Li et al. ^[1]. The researchers performed a prospective, double-blinded, and double-simulation study on the efficacy of Modified Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GERD) and its effect on esophageal motility. The study enrolled 288 participants with GERD, and then divided them into the treatment and control groups, receiving MXD plus omeprazole simulation and omeprazole plus MXD simulation, respectively, for 4 weeks. The GERD-Q scale score and esophageal manometry were evaluated. The result showed that MXD had a similar ability to increase the pressure at the lower esophageal sphincter and reduce ineffective swallowing, compared with omeprazole in mild-to-moderate GERD. The recurrence rate was significantly lower than that of the control group within 3 months, on follow-up visits. We greatly appreciate the dedication of the authors towards studying the effect of MXD

on GERD as an optional therapy. (the actual study design)

As we all know, GERD has a high global prevalence with limited therapeutic options, and its incidence is increasing annually. Patients with GERD present with variety of symptoms including heartburn, effortless regurgitation, dyspepsia, bloating, and abdominal pain or discomfort as well as cough and laryngitis, which severely impact their quality of life^[2]. Since the 1990s, proton pump inhibitor (PPI) therapy has evolved as the standard treatment of choice for GERD^[3]. However, it has become evident that symptoms attributed to GERD remain despite ongoing PPI treatment in up to 40% of patients^[4], and PPI increases the risks of infections, osteoporosis, hepatic failure, pancreatitis, jaundice, and persistent gynecomastia^[5-7]. Therefore, multivariable treatment beyond PPI is urgently required. (the status of problem)

Traditional Chinese Medicine believes that the herb Chaihu could regulate qi-flow to harmonize digestive disorders. The formula Xiaochaihu Decoction, which has demonstrated therapeutic effects such as for nausea, poor appetite, and epigastric distension, has been used in treating GERD for thousands of years in Asian countries. However, high-level evidence-based Traditional Chinese medical research is still lacking and is restricted by many factors. For instance, the herb formula is customized according to patient characteristics including severity of disease, gender, and age. Besides, pharmaceutical effects may be influenced by the way Chinese herbs are decocted. Thus, it is hard to provide the same drug dose for each patient. (the status of problem) In this research, drug selection of herbal granule makes double-blind research achievable. For the concealed allocation, herbal granules were supplied instead of traditional decoction, which greatly reduced the bias from herb treatment.

A limitation of this study was a lack of record keeping of the side effects and rescue medications. With the growing popularity of traditional Chinese medicines, reports of herbal side effects are common. Bupleurum, the main

component of MXD, was found to increase the risk of chronic hepatotoxicity [8, 9]. Meanwhile, Itoh et al. reported that long-term oral administration of MXD caused cholestatic liver injury, interstitial pneumonia, and even death [10]. Therefore, medical safety evaluation tests, such as liver and kidney function indices, should be assessed. Rescue medication or treatment for these adverse events should also be considered. (the strength and limitation of the study).

Besides, although the sample size was well calculated according to previous literature reports and formula, the sample size for esophageal manometric indicators, which was from 7-52, was relatively small. (the strength and limitation of the study).

The authors mainly focused on the efficiency of MXD therapy for a short duration. As we know, GERD is generally a chronic disease with recurrent symptoms and requires long-term management [11]. (the strength and limitation of the study). Further studies are needed to evaluate the effects of prolonged MXD therapy on GERD rehabilitation. (future directions).

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript, a letter to editor, provided reasonable suggestion to a published clinical study evaluating the efficacy of Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GERD). It can be considered for publication with some revision. The abstract does not seem to be a good summary of the main content of the manuscript and thus need to be improved; The "Core Tips" part is also suggested to rewrite the sentences reasonably in a logical order; The main content of the manuscript is also suggested to rewrite and highlight the explanation of the reason for the recommendations and thus the suggestions on sample size, adverse reaction and the effects of prolonged MXD therapy can be clearly presented for readers. The Logical association between treatment risk in GERD of Proton pump inhibitors (PPIs) and MXD need to be clearly presentd, if it does exist.

A: The paper was rechecked by a native speaker in order to improve language quality.

Thank you for the recommendation.

We rewrite the abstract text. (added words are in red color)

Old version

Gastroesophageal reflux disease (GERD) has a high prevalence worldwide and limited therapeutic options. A clinical study by Li et al. provided us with a new treatment choice for GERD, Xiaochaihu Decoction.

New version

Gastroesophageal reflux disease (GERD) has a high prevalence worldwide and limited therapeutic options. Modified Xiaochaihu Decoction (MXD) by Li et al., a new therapy for GERD, is a well-designed study that minimizes bias of herb dose. Their research showed MXD had similar therapeutic effect to omeprazole in mild-to-moderate GERD. One limitation of this study was that it lacked records of side effects and rescue medication. As a chronic disease with recurrent symptoms, GERD rehabilitation requires prolonged observation of the clinical course with MXD therapy.

We rewrite the core tip text. (added words are in red color)

Old version

The therapeutic effects of Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GRED) have been demonstrated for thousands of years in Asian countries. Li et al. conducted a well-designed clinical study evaluating the efficacy of MXD for GERD. High-quality randomized controlled trials require a larger number of patients, and it is important to record the side effects of MXD in this study. Rescue medication or treatment should also be considered. Further studies are needed to examine the effects of prolonged MXD therapy on GERD rehabilitation.

New version

Modified Xiaochaihu Decoction (MXD) has been applied for gastroesophageal reflux disease (GRED) for thousands of years in Asian countries. Li et al. conducted a well-designed clinical study and proved that MXD was an ideal

optional therapy for GERD. The drug selection of herbal granule makes double-blind research achievable. Side effects and rescue medication should be noted. As a chronic disease, GERD rehabilitation requires prolonged observation of the clinical course with MXD therapy.

We rewrite the main text. (added words are in red color)

Old version

We read with interest a clinical study by Li et al.^[1]. The researchers performed a prospective, double-blinded, and double-simulation study on the efficacy of Modified Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GERD) and its effect on esophageal motility.

GERD has a high prevalence worldwide with limited therapeutic options, and its incidence is increasing annually. Traditional Chinese Medicine believes that the herb Chaihu could regulate Qi-flow to harmonize digestive disorders. The formula for Xiaochaihu Decoction, which has demonstrated therapeutic effects for nausea, poor appetite, epigastric distension, etc., has been applied for treating GERD for thousands of years in Asian countries. However, high-level evidence-based medical research is still lacking. Li et al. conducted a well-designed clinical study evaluating the efficacy of MXD for GERD and its effect on esophageal motility. Although the number of cases at secondary endpoints was low, the study results suggest that MXD could have therapeutic effects in GERD. High-quality randomized controlled trials require a larger number of patients.

However, it is important to record the side effects in this clinical study. Proton pump inhibitors (PPIs), a standard treatment strategy for GERD, increase the risk of infections, osteoporosis, hepatic failure, pancreatitis, jaundice, and gynecomastia^[2-4]. MXD may also cause additional side effects. Li et al. summarized the increased risk of overdose-induced acute or accumulation-related chronic hepatotoxicity of Bupleurum^[5]. Furthermore, Lee et al. reported a higher risk of liver diseases in their clinical observations in patients who used MXD or a high dose of Bupleurum^[6]. Meanwhile, Itoh et

al. reported that long-term oral administration of MXD causes cholestatic liver injury, interstitial pneumonia, and even death^[7]. Therefore, medical safety evaluation tests, such as liver and kidney function indices, should be assessed. Rescue medication or treatment should also be considered. The authors mainly focused on the efficiency of MXD therapy for a short duration. Further studies are needed to examine the effects of prolonged MXD therapy on GERD rehabilitation.

New version

We read with interest a clinical study by Li et al. ^[1]. The researchers performed a prospective, double-blinded, and double-simulation study on the efficacy of Modified Xiaochaihu Decoction (MXD) for gastroesophageal reflux disease (GERD) and its effect on esophageal motility. The study enrolled 288 participants with GERD, and then divided them into the treatment and control groups, receiving MXD plus omeprazole simulation and omeprazole plus MXD simulation, respectively, for 4 weeks. The GERD-Q scale score and esophageal manometry were evaluated. The result showed that MXD had a similar ability to increase the pressure at the lower esophageal sphincter and reduce ineffective swallowing, compared with omeprazole in mild-to-moderate GERD (the explanation of the reason for the recommendations). The recurrence rate was significantly lower than that of the control group within 3 months, on follow-up visits. We greatly appreciate the dedication of the authors towards studying the effect of MXD on GERD as an optional therapy. (the actual study design)

As we all know, GERD has a high global prevalence with limited therapeutic options, and its incidence is increasing annually. Patients with GERD present with variety of symptoms including heartburn, effortless regurgitation, dyspepsia, bloating, and abdominal pain or discomfort as well as cough and laryngitis, which severely impact their quality of life ^[2]. Since the 1990s, proton pump inhibitor (PPI) therapy has evolved as the standard

treatment of choice for GERD [3]. However, it has become evident that symptoms attributed to GERD remain despite ongoing PPI treatment in up to 40% of patients [4], and PPI increases the risks of infections, osteoporosis, hepatic failure, pancreatitis, jaundice, and persistent gynecomastia [5-7]. Therefore, multivariable treatment beyond PPI is urgently required. (the status of problem, the explanation of the reason for the recommendations, the Logical association between treatment risk in GERD of Proton pump inhibitors (PPIs) and MXD)

Traditional Chinese Medicine believes that the herb Chaihu could regulate qi-flow to harmonize digestive disorders. The formula Xiaochaihu Decoction, which has demonstrated therapeutic effects such as for nausea, poor appetite, and epigastric distension, has been used in treating GERD for thousands of years in Asian countries. However, high-level evidence-based Traditional Chinese medical research is still lacking and is restricted by many factors. For instance, the herb formula is customized according to patient characteristics including severity of disease, gender, and age. Besides, pharmaceutical effects may be influenced by the way Chinese herbs are decocted. Thus, it is hard to provide the same drug dose for each patient. (the status of problem) In this research, drug selection of herbal granule makes double-blind research achievable. For the concealed allocation, herbal granules were supplied instead of traditional decoction, which greatly reduced the bias from herb treatment.(highlight the explanation of the reason for the recommendations)

A limitation of this study was a lack of record keeping of the side effects and rescue medications. With the growing popularity of traditional Chinese medicines, reports of herbal side effects are common. Bupleurum, the main component of MXD, was found to increase the risk of chronic hepatotoxicity [8, 9]. Meanwhile, Itoh et al. reported that long-term oral administration of MXD caused cholestatic liver injury, interstitial pneumonia, and even death [10]. Therefore, medical safety evaluation tests, such as liver and kidney function indices, should be assessed. Rescue medication or treatment for these adverse events should also be considered. (the strength and limitation of the study,

suggestions on adverse reaction).

Besides, although the sample size was well calculated according to previous literature reports and formula, the sample size for esophageal manometric indicators, which was from 7–52, was relatively small. (the strength and limitation of the study, suggestions on sample size).

The authors mainly focused on the efficiency of MXD therapy for a short duration. As we know, GERD is generally a chronic disease with recurrent symptoms and requires long-term management ^[11]. (the strength and limitation of the study). Further studies are needed to evaluate the effects of prolonged MXD therapy on GERD rehabilitation. (future directions, suggestions on the effects of prolonged MXD therapy).

At last, I would like to appreciate your guidance and say thank you for all your recommendations. Please feel free to let me know if any further changes required. I am looking forward to seeing you your reply.