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Response to Editors and Reviewer's comments

Dear Editor and Reviewers,

Thanks very much for your valuable comments and suggestions, which have furtherly improved our manuscript.

Please find enclosed the reviewers' suggestions and our specific responses to the comments. We have adjusted the manuscript in accordance with the suggestions and comments of the reviewers and the Science Editor. We revised our manuscript according to the BPG formatting guidelines for Randomized Controlled Trial. We provide the original figures that can be reprocessed by the editor. PMID and DOI were added in the reference list and all authors of the references were listed. The "article highlight" section were added at the end of the main text. We hope that the editorial board will appreciate our work and accepts our revised manuscript for publication in World Journal of Gastroenterology.

Yours sincerely,

On behalf of all authors,

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Reviewer #1:

It is quite normal that a western reviewer has some problems to understand the arguments of TCM, e.g. the importance of the different qis. However, it is interesting how a possible bridge can be built between TCM and western medicine. In the present manuscript the authors used RomeIV criteria and TCM criteria, but finally in the evaluation they focus on Rome IV criteria and a visual analouge scale. Therefore, I surmise that the conclusions drawn from this study are correct. I have only minor points of criticisms: Evidently the authors used only the dose of 5 g TID. Is there a dose-dependency of the effects? An analysis of the different components of the product and the possible modes of action are indicated. How were this data obtained? Why were Talcid used a sa rescue drug? Would it be fine to perform a study comparing BLWTG with PPI?

Response to Reviewer #1

Thank you very much for your comments. Please see below one by one response to the comments.

1.Evidently the authors used only the dose of 5 g TID. Is there a dose-dependency of the effects?

Response: Based on the previous clinical experience, we only set a 5g TID dose group, but no other dose groups. Thus, we were unable to show the dose-dependency of the effects of BLWTG treatment for epigastric pain syndrome.

Multiple-dose, parallel-group designs for observing the dose-dependency effect are seldom adopted in the clinical studies on traditional Chinese medicine (TCM), especially in the clinical research of compound traditional Chinese drugs with multiple components. The TCM prescriptions and their



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doses are based on the accumulated experience of outstanding TCM physicians in treating patients and the records in TCM classics. Similarly, the daily dose of BLWTG was determined on the basis of the TCM prescriptions, and its efficacy was validated according to the dosage used in the clinical patients.

2. An analysis of the different components of the product and the possible modes of action are indicated. How were this data obtained?

Response: These data were obtained from the previously reported animal experiments.

3. Why were Talcid used as a rescue drug?

Response: Talcid is mainly used to treat an upset stomach and indigestion, including stomachache, heartburn, acidic belching, and fullness. It has an obvious antacid effect and also can protect mucous membrane. With a fast but gentle effect, it can be used to alleviate symptoms of epigastric pain syndrome and serve as a rescue (supplementary) drug as well.

4. Would it be fine to perform a study comparing BLWTG with PPI?

Response: Epigastric pain syndrome is a functional gastrointestinal disease. According to Rome IV, a placebo-controlled design is frequently used in clinical studies, which is also the reason why we adopted this design in our study. Undoubtedly, PPI is a well-recognized treatment in suppressing stomach acid, and BLWTG might not be definitely better than PPI in the treatment of epigastric pain syndrome. However, according to the recent literature, there are safety issues associated with PPI, such as gastric fundus polyps (Tran-Duy, An, et al. 2016. Use of Proton Pump Inhibitors and Risks of



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Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. *Clinical Gastroenterology & Hepatology* 14.12:1706-1719.e5), atrophic gastritis (Li, Zhong , et al.2017.Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis.*Saudi Journal of Gastroenterology* 23.4:222-228), gut microflora dysfunction and diarrhea after C. difficile infection (Center for Drug Evaluation and Research. Drug Safety and Availability - FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs)), and cardio-cerebrovascular events (Mark, et al.2012. Optimal Management of Antiplatelet Therapy and Proton Pump Inhibition Following Percutaneous Coronary Intervention. *Current Treatment Options in Cardiovascular Medicine*). Our study has suggested that BLWTG is a good option for the treatment of epigastric pain syndrome. Parallel controlled studies comparing BLWTG and PPI may be carried out in future.

Reviewer#2:

This is a well-designed and executed double-blind trial controlling traditional Chinese medicine (TCM), a very rare fact even though TCM have been applied for centuries in large numbers of population, and there are large numbers of medical doctors in China who have deep knowledge of western medicine and methodology. I would encourage the authors to proceed with a similar trial not with placebo this time, but with drugs applied in everyday practice in western medicine, and with larger sample of patients in order to avoid subgroup analysis.

Response to Reviewer #2

Response: Thank you for your comment. Epigastric pain syndrome is a



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functional gastrointestinal disease. According to Rome IV, a placebo-controlled design is preferred in clinical studies, which is also the reason why we adopted this design in our study. There is no doubt that the role of PPI in suppressing stomach acid has been well recognized, and BLWTG might not be definitely better than PPI in the treatment of epigastric pain syndrome. However, recent literatures have also reported the safety issues associated with PPI, such as gastric fundus polyps (Tran-Duy, An, et al. 2016. Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. *Clinical Gastroenterology & Hepatology* 14.12:1706-1719.e5), atrophic gastritis (Li, Zhong, et al. 2017. Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis. *Saudi Journal of Gastroenterology* 23.4:222-228), gut microflora dysfunction and diarrhea after *C. difficile* infection (Center for Drug Evaluation and Research. Drug Safety and Availability - FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs)), and cardio-cerebrovascular events (Mark, et al. 2012. Optimal Management of Antiplatelet Therapy and Proton Pump Inhibition Following Percutaneous Coronary Intervention. *Current Treatment Options in Cardiovascular Medicine*). Our study has suggested that BLWTG is a good treatment option for epigastric pain syndrome. Parallel controlled studies comparing BLWTG and PPI may be carried out in future to identify the patients who will benefit most from BLWTG and set the precise dose ranges. The limitation was described in revised manuscript in blue, Page 16.