

Format for ANSWERING REVIEWERS

February 22, 2014

Title: Endoscopic papillary large balloon dilation versus endoscopic sphincterotomy for retrieval of choledocholithiasis: A meta-analysis

Author: Piaopiao Jin MD; Jianfeng Cheng MD,PhD; Dan Liu MS ; Mei Mei MD; Zhaoqi Xu, MD; Leimin Sun MD,PhD

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6250

Jianfeng Cheng MD, Ph.D: WJG Number ID: 00069475

Leimin Sun MD, Ph.D: WJG Number ID: 01560081

Dear Editor,

We thank the reviewers and editors of World Journal of Gastroenterology for their constructive review and comments. We believe the manuscript is significantly improved thanks to these comments. We have incorporated all the suggestions made by the reviewers and hope the manuscript is now considered suitable for publication. Below please find our responses to the individual comments.

Part A. Reviewer NO 02549970

- 1) Comment 1: "Finally, 7 randomized clinical trials with 868 subjects met the inclusions" they have to mention the references.

Response: Thanks for the reviewer's excellent suggestion. In our original draft, there were 7 trials with 3 abstracts included. One of the reviewers provided us valuable suggestion that abstracts included might affect the quality of the meta-analysis and should be excluded. We fully agree with this suggestion even though no substantial changes were found in the sensitivity analysis by excluding 3 abstracts which might cause potential bias. It is possible that the incomplete information of abstract might affect the accuracy and reliability of the meta-analysis. We searched the database again and found one full text of Bo Q J. Therefore, we excluded the two meeting abstracts without full text and included 5 clinical trials with full text. In the current revised manuscript, there were five randomized controlled trials with 621 participants included. The baseline characteristics of 5 trials were shown in table 1 in detail. Quality assessment showed a high quality of all the 5 RCTs included (shown in table 2). In addition, the new pooled outcome was similar to the original one, but with better homogeneity in both primary outcome and secondary outcome (shown in table 3). The reference has been added to into the paper (Page7, paragraph 4).

- 2) Comment 2: Authors are mentioning in the introduction that "but also long term adverse event like sphincter dysfunction" in the 1st paragraph in the introduction section but they didn't report it in the result.

Response: We appreciate about this very constructive suggestion. We apologize that we couldn't report the long term outcome such as sphincter dysfunction since there was no data about this mentioned in the 5 trials included in our meta-analysis because of the short duration of follow-up. We do think the reviewer's suggestion was very important and valuable. We searched for the relevant information in the database. It has been added to the page 12, paragraph 2. It is said "EPLBD might not preserve the function of oddi sphincter, but would result in an even worse condition than EST and the pressure

gradient between the CBD and the duodenum is likely to eliminate after EPLBD". More clinical trials like RCTs are recommended to confirm this conclusion.

- 3) Comment 3: Authors mentioned 7 articles, why did they have to choose articles with abstract only?

Response: Thanks very much for the reviewer's comments. We fully agree with the suggestion and excluded the two meeting abstract in the revised manuscript so as to improve the quality of the meta-analysis. The new pooled outcome in the revised manuscript showed no substantial changes to the original ones, but with better homogeneity. Now, we believe that the revised manuscript was more accurate and reliable.

- 4) Comment 4: In the 1st paragraph under " Complete stone removal rate: they mentioned 6 articles.....the same happen under section of" Complete duct clearance in one session:.....and under section of " Overall adverse events:

Response: Thanks for the reviewer's kind suggestion. We apologize for the confusion caused by forgetting to label the reference. In the revised manuscript, all the trials included reported the outcome of EPLBD and EST in complete stone removal rate, complete duct clearance in one session and overall adverse events.

- 5) Comment 5: Authors reporting that the diameter of balloon is varying from 12-20mm..... is this could be applicable for any CBD diameter ?????

Response: Thanks very much for the reviewer's comment. This question is very important and meaningful. As a new technique, we need to be familiar with its indication. So in the revised manuscript, we mentioned that "patients targeted for EPLBD may be those with CBD dilation but without strictures of the distal CBD and the size of the selected balloon shouldn't exceed the maximal diameter of common bile duct" (Page14, paragraph 2). According to the review of Lee D K (reference 35), the stricture of the distal CBD may increase the chance of perforation of EPLBD and the size of the balloon should be chosen based on the maximal diameter of stones and the diameter of CBD.

- 6) Comment 6: under section of " Overall adverse events: In 4 RCTs [14, 15, 25] there are three references..... while in the other three abstracts [16, 17, 26, 27], there are 4 references.

Response: We are grateful for your cautious peer review. We apologize for the mistake. In the revised manuscript, the morbidity in the 5 RCTs included was all diagnosed according to the Cotton consensus. Page10, paragraph 1).

- 7) Comment 7: Hemorrhage was defined as a decrease in hemoglobin concentration of >2 mg/dl.....what is the unit for hemoglobin concentration????

Response: Thanks for the reviews kind remind. We have revised the unit of the hemoglobin (2g/dl in Page10, Paragraph 2).

- 8) Comment 8: There are some minor language polishingThe 5th paragraph in discussion....." make the papillary orifice palutous" ..needs correction Also...in the authors contribution.

Response: Thanks for the reviewer's kind suggestion. We have polished the language according to the requirement of WJG. Now, we believe the revised manuscript is more integrated and informative based on the valuable feedback.

Special thanks to you for your very suggestive comments.

Part B Reviewer 02459732

- 9) Comment 9: Piaopiao Jin et al. has conducted a meta-analysis to compare the safety and effectiveness of endoscopic papillary large balloon (EPLBD) dilation with endoscopic sphincterotomy(EST) in retrieval of choledocholithiasis. After involving 7 RCTs, they conducted

EPLBD could be advocated as an alternative to endoscopic sphincterotomy in the retrieval of large bile duct stones. One major concern: 3 of the 7 included RCTs were abstract without full text. It is impossible to evaluate study quality of these 3 RCTs. During conducting a meta-analysis, authors should know that study quality and bias could impact and jeopardize the reliability of conclusion. Therefore, these 3 RCTs should not be involved in this review. In addition, more attention about limitation should be paid in the Discussion Section.

Response: Thanks for the reviewer's very constructive suggestion. We fully agree and excluded the studies with only abstract available from our analysis and re-analyzed the five RCTs with full text. All the RCTs included in our analysis achieved a score higher than 3' in the quality assessment. The new outcomes showed similar conclusion to the original one, but with smaller heterogeneity (in table 3). Then in the part of the sensitivity analysis, we reanalyzed the data by switching to another statistical effect model (eg. Switch the fixed effect model to the random effect model). The result was stable. Therefore, we believe that the revised meta-analysis is more reliable.

In the discussion, we discussed the potential bias of different operation of EPLBD (EPLBD alone or EPLBD plus EST), and the limited number of RCTs. In addition, EPLBD was mostly applied in the East Asian country, like Korea and China. The five RCTs were mainly carried out in Korea and China. Therefore, data from Europe, United States and other countries are further required to confirm the efficacy and safety.

Part C Reviewer 02512856

- 10) 1. This article needs a great deal of language polishing. I will deal with several examples and then I will point out some parts of the manuscript that need complete rephrasing to improve understanding.

Page 3: with the same uniforms- it should say instead "using the same criteria"

Page 4: it was involved with a maximal papillotomy- "it involved a maximal papillotomy".
10-15% stones were failed to be removed by the either technique above- "10-15% of the stones could not be removed by either of the above-mentioned techniques.

Page 5: on an account of-"on account of". Adverse event- "adverse events".

Page 7: By searching the database...- "The search of the above-mentioned database yielded 715 articles". 504 were further excluded to review, case series...- "504 were further excluded for the following reasons:".

Page 8: literatures- "literature". In the Figure 1- "in Figure 1". In the Table 1-"in Table 1".
Was found in the either two aspect...- "was found in either of the aspects..."

Page 9: as shown Table 4- "as shown in Table 4".

Page 10: So it was wondered whether...-"This raised the question whether...". The need of mechanical lithotripsy in our review was significantly reduced in EPLBD than EST- "The need for mechanical lithotripsy in our review was significantly reduced in EPLBD compared to EST".

Page 11: Moreover, pancreatitis happened to the included patients...- "Moreover, pancreatitis occurring in some of the patients studied".

Page 12: were failed to be compared-"could not be compared".

Page 13: and the pressure gradient between the CBD and the duodenum is likely to eliminate...-" and the pressure gradient between the CBD and the duodenum will probably be eliminated". As a result, funnel plot was failed to be performed-"could not be performed...". Researches, especially from western countries are deserved...- "research, especially from western countries is warranted...".

Page 15: Endoscopic papillary balloon dilation is a technique involves dilation of ...- "Endoscopic papillary balloon dilation is a technique that involves dilation of".

Parts of the manuscript that require complete rephrasing:

Page 9: under "Subgroup analysis". "It was declared..."

Page 11: "Once large balloon...". "With the precut remained..."

Page 13: "It is important...Since one study...". This sentence is too long and does not make

- any sense. Consider rephrasing: "In fact, one study carried out on 200 consecutive patients...".
2. The authors use "statistically significant" too often. As this article is a meta-analysis and use a lot of statistics, it could be omitted as it is implied.
 3. Page 6 (under "Study selection"): consider "Randomized controlled trials with a full test available...".
 4. Page 14: As we all know, this is the first meta-analysis that compared EPLBD with EST based on the five RCTs. Consider "As we all know, this is the first meta-analysis to compare EPLBD with EST based on five RCTs.
 5. Page 15 (under "Terminology"). Each paragraph describes an endoscopic technique. Consider using the colon in each paragraph or either not using it in paragraph 3.
 6. Page 21 (Figure 1). When it says "43 articles excluded for the following reasons" it should say "45 articles excluded for the following reasons".
 7. Page 24 (Table 1). In Table 1 the authors use three different acronyms: LBD, EBD and EPLBD. Please, clarify. I would suggest that the authors use only EPLBD, otherwise it causes confusion.
Page 24, at the bottom right corner. Please correct "thid". It should say "third"
 8. Page 26 (Table 2). I like this table very much.

Response: We are very grateful for the reviewer's valuable advice. First, we have revised all the language problems pointed out by the reviewer (See the red font in the manuscript). Second, we admitted that the phrases "statistically significant" might be used too often. So we have tried to omit these words. Now, this phrase has only been used twice in the new manuscript (see the blue underlined fonts). However, despite a lot of statistics used in the meta-analysis, we suppose that "significantly difference" could used simultaneously, in the light of the former published meta-analysis. Third, in Page 15 (under "Terminology"), we have added the colon in each paragraph to introduce the endoscopic technique. Forth, we have updated the figure1 in Page 21. Finally, the acronyms "LBD, EBD and EPLBD" in Page 24 (Table 1) are different ways of expression of "endoscopic papillary large balloon dilation" in the included RCTs. We kept them in order to respect the originality of the included RCTs. We felt sorry for the confusions made by us and we used only EPLBD in the new table 1. We believe the current meta-analysis is articulate and integrated.

References and typesetting were corrected accordingly.

We appreciate the opportunity for publishing this meta-analysis in the World Journal of Gastroenterology.

Sincerely yours,

Sun LM, MD, PhD
Department of Gastroenterology,
Sir Run Run Shaw Hospital,
School of Medicine, Zhejiang University, Hangzhou, China
Fax number: +86 571 8600 6186

sunleimin@yahoo.com