

Manuscript NO: 60883

Title: Could Saline Irrigation Clear All Residual Common Bile Duct (CBD) Stones After Lithotripsy? a self-controlled prospective cohort study

Dear editors,

Thanks for your decision letter and for the reviewers' comments concerning our manuscript entitled "Could Saline Irrigation Clear All Residual Common Bile Duct (CBD) Stones After Lithotripsy? a self-controlled prospective cohort study" (Manuscript NO: 60883). Those comments are all valuable and very helpful to revising and improving our article, and emerge as the important guiding significance to our researches as well. We have read the comments carefully and have made some corrections which we hope could meet with approval. The main correction in the paper and our responses to the reviewer's comments and editor's suggestions are as following:

Round-1

Reviewer #1: The article deals with very interesting topic associated with saline irrigation after complete removal of choledochal stones confirmed by cholangiographic imaging.

I guess, however, there are some points to be modified.

1. The protocol of cholangiographic evaluation and irrigation procedure seems to be difficult to understand. Description of the protocol should be clearly described in order to make you method easier to understand.

Response: Thank you for the comment. We've revised the article and added a flowchart accordingly.

2. In addition, as the study dealt only with the subject who underwent lithotripsy, it should be clearly mentioned not only in 'Introduction' but also in 'Material and methods'.

Response: We've detailly described the subjects who received lithotripsy both in the introduction part and the materials and methods part.

3. Further, I encourage the authors to add a flow chart showing the protocol of evaluation and irrigation procedures.

Response: Thanks for the comment. We've added a flowchart to the materials and methods part.

4. The authors mention, 'The CBD clearance score was assessed by two blinded endoscopists.' How did you determine a final score for each evaluation? Please explain. What about the reproducibility of CBD clearance score by two evaluators?

Response: We've established a stone clearance scoring system. Two endoscopists were masked and performed the scoring separately. The mean value was then calculated and rounded to the nearest integer. The reproducibility of CBD clearance score by two endoscopists can reach a favourable score agreement value higher than 80%.

5. Acute cholangitis has long been diagnosed on the basis of Charcot's triad. However, Charcot's triad has significant problem with a low sensitivity [1]. Thus, TG13 [1] has been more widely used as a criterion for acute cholangitis in many studies. [1] Kiriya S et al. J Hepatobiliary Pancreat Sci 2013; 20: 24-34.

Response: Thanks a lot for your advice. We've made corrections and added relevant references.

6. The use of cholangioscopy and saline irrigation is reportedly a risk factor of cholangitis after ERCP. Some previous reports indicated the efficacy of antibiotic for reducing the risk of cholangitis. The use of antibiotics, including prophylactic use should be mentioned in the text.

Response: We have described the use of antibiotics in the manuscript. (Please see Procedures).

7. Please explain the method of lithotripsy for patients participating the present study. Did any patients undergo cholangioscopic lithotripsy with laser and/or EHL? Please mention the situation.

Response: Lithotripsy was performed using an endoscopic lithotripter-compatible basket. No patients underwent cholangioscopic lithotripsy with laser and/or EHL.

8. If you failed to stone clearance with a saline of 100 ml, saline irrigation continued until getting the score 5. Please include more information about the patients required additional irrigation over 100 ml. How much saline solution did they need for complete clearance?

Response: If stone residuals were not completely removed after two times of 50 ml saline irrigation, an extra 50-100 ml saline was then used to remove the remaining stone residuals.

9. Your conclusion includes patients with PAD and/or a dilated CBD may not completely clear residual choledochal stones after lithotripsy. What is possible reason for more necessary irrigation for complete clearance in patients with such condition? Please discuss.

Response: Thank you for pointing out this important issue, which we have discussed in detail in the discussion part.

10. Your last assessment, the correlation between the compositions of stones and variables, is not related to the main topic and appears to be redundant. I think the last assessment should be eliminated from the study.

Response: Thank you for the comment. We wish to retain the last assessment. We found that soft bile pigment stones produce small fragments or debris after mechanical lithotripsy, and inadequate irrigation can cause stones to remain, so there is a correlation between stone composition and irrigation volume.

Reviewer #2

1. I thank the editor in chief for assigning me the revision of this paper. It deals with a subject of considerable importance. As the authors pointed out in the introduction, the management of incomplete gallbladder removal following open and laparoscopic techniques has been addressed in several studies.

2. Although the author submitted a well-written paper I struggle to find original findings. One aspect that I have doubts about is the structure of the paper. The authors, in fact, after having 'built a score' apply it to the evaluation of CBD. Perhaps this artifice needed to be better explained.

Response: Thank you for the comment. In fact, we used the CBD Clearance system to guide our saline irrigation, and we also compared the scores for different irrigation volumes.

In addition, we have added a flowchart showing the protocol of evaluation and irrigation procedures.

3. Another concern: What was the irrigation pressure? High pressure can induce/precipitate cholangitis.

Response: Our method: A 20ml syringe was manipulated by the assistant. After 5ml saline was rapidly injected, there was 1-second pause. This procedure was repeated until all 20ml saline was injected. Due to an ideal pressure monitoring method was not available at the time, the irrigation pressure data was not recorded.

Indeed, high bile duct pressure resulted from saline irrigation is a risk factor of post-operative cholangitis. Our data showed that the post-operative cholangitis rate was not elevated in this group of patients. Possible reasons include: 1. The irrigation was performed intermittently. Also, the suction force applied to the duodenoscope promoted saline drainage. Therefore, very few amounts of saline were able to reach the intrahepatic bile duct. 2. Antibiotics was routinely administrated prophylactically. 3. Plastic stent placement or Endoscopic nasobiliary drainage (ENBD).

4. While the proposed technique appears to be effective, the authors themselves point out that the approach cannot be routinely used as 'with the SpyGlass DS increases the procedure

time with additional costs'. This approach allowed to demonstrate the study hypothesis but limits the quality and importance of this manuscript.

Response: SpyGlass DS indeed increased the procedure time and costs, but the purpose of our study is not encouraging SpyGlass assessment for all patients who received lithotripsy. And our results showed that 100ml saline irrigation after lithotripsy increased CBD stone clearance rates.

5. In brief: the article is well written and confirms that good irrigation is effective to improve CBD clearance especially in case of biliary tract dilation or PAD. What is the novelty?

Response: Lithotripsy for large CBD stone may cause a large amount of stone residues. These residues were mostly not shown even on Occlusion cholangiography. But the stone residuals were still observed by SpyGlass DS system in our study. We found that 50-100ml saline irrigation after lithotripsy increased CBD stone clearance rates. Importantly, the purpose of our study is not encouraging SpyGlass assessment for all patients who received lithotripsy. Instead, based on results from our study, we recommend our saline irrigation method to be applied to decrease stone recurrence rates after lithotripsy.

Round-2

It is revised accordingly and became easier to understand. However, only one more revision is required as indicated below. P.8, L.12 'SpyGlass' (Boston Scientific Corporation, Marlborough, Massachusetts, USA) should be 'SpyGlass DS'.

Response: We have revised accordingly in P.8, L.12. 'SpyGlass' has been changed to 'SpyGlass DS'.

Thank you for your suggestions. We hope that the revision is acceptable, and I look forward to hearing from you soon.

Best wishes,

Yours sincerely,

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