

Dear reviewer and editor,

I really appreciate your insightful and detailed suggestions and comments on our manuscript, and I did find the whole article more logical and scientific after modified according to your reviews. Following is the response (the reviewer's comments are in orange). Modifications were quoted after the "Authors' Response" and highlighted in the manuscript.

INTRODUCTION

1) "Tumors of the main duodenal papilla are rare, with a prevalence of only 0.04% to 0.12% in autopsy studies." Include the reference of these studies.

Authors' Response: Thanks for your reminder. References were included in the text respectively. (*page 5, line2*)

2) "potentially develop into adenocarcinoma through the adenoma-adenocarcinoma sequence." Include the reference.

Authors' Response: Thanks for your reminder. References were included in the text respectively. (*page 5, line 4*)

3) "Pancreaticoduodenectomy and endoscopic papillectomy (EP) are the main treatments of PA, and EP is more recommended for benign papillary lesions because of its advantages over open surgery, including less trauma, satisfying treatment outcomes, fewer adverse events and lower cost." Reference

Authors' Response: Thanks for your reminder. References were included in the text respectively. (*page 5, line 9*)

4) “, endoscopists also found intraoperative and postoperative adverse events.” Did endoscopists find adverse events intraoperatively? What did you mean by that? A surgeon who is also an endoscopist? I think you should review that sentence.

Authors’ Response: Sorry for the confusion. What I mean is that surgeons found adverse events. A correction was made in the manuscript. Thanks for your suggestion. (*page 5, line 11*)

5) “These included frequent bleeding” Frequent bleeding? Are you sure about this? What is the reference for this?

Authors’ Response: We believe that bleeding is relatively frequent compared with other EP-related adverse events and more frequent after EP than after other endoscopic treatments. However, considering the morbidity of post-EP bleeding (around 4.5%-45%), “frequent” may be not very proper. Thus, we modified this part in the manuscript (*page 5, line 12*)

Modification: These included bleeding, operation-related pancreatitis, perforation

6). “In our over 15-year experience with EP application, bleeding and perforation occurred in several patients postoperatively, and these events did lead to extremely difficult results that needed invasive surgical intervention or even resulted in death, although this was not common.” We do not want to know your experience in introducing the topic, in introducing your article. If you want to express it, include it in the speech.

Authors’ Response: Thanks for your reminder. We have made some modifications to this part to make it more concise. (*page 5, paragraph 2*)

Modification: These adverse events could lead to extremely difficult results

that require invasive surgical intervention or even result in death, although this is not common but does limit the wide application of EP.

7) At the end of your introduction you must include your objective. Make that clear.

Authors' Response: Thanks for your suggestion. We have made some modifications to this part to present our objective in a clearer way. (*page 5, paragraph 3*)

Modification: To decrease the postoperative adverse event rate of EP and improve patients' postoperative condition, we modified conventional endoscopic papillectomy and initiated a novel method and procedure for endoscopic papillectomy in 2016. To verify the safety and feasibility of this novel method, we reviewed the outcomes of patients undergoing novel or conventional EP.

MATERIALS AND METHODS

8) You did not make it clear in the text that your study is not blind randomized. Make that clear.

Authors' Response: Thanks for your reminder. We have modified this part to make it clear. (*page 6, line 8-9*)

Modification: As a retrospective observational study, the study was not blind randomized.

9) You did not make it clear in the text that there was a sample calculation and how you arrived at this number. Explain the limitations of the study as to why you have not divided the groups correctly.

Authors' Response: Thanks for your reminder. We added the sample calculation method and result in the text (*page 6, line 6-8*). We addressed this limitation in the discussion part and explained the reason is that this study is a retrospective study and the sample selection was not well-planned before the initiation of the study. (*page 13, paragraph 2*)

Modification: Sample size calculation with the adverse event rates of two groups (significance level of 5% and power of 80%) suggested a minimum sample size of 70. (*page 6, line 6-8*)

As a retrospective study, there are some limitations: (1) this study was not blind randomized; and (2) the sample size was not large enough, although it reached the minimum calculated sample size, the samples were not divided evenly between the two groups. (*page 13, paragraph 2*)

10) You describe the procedure and, without any division, describe the statistical tests. Leave it separate.

Authors' Response: Thanks for your reminder. I divided these two parts with "Statistical methods" in the text. (*page 7, line 11*)

RESULTS

11) "and they were grouped by novel or conventional methods" Make it clear to your readers how the division between groups was made, who chose, and how it happened.

Authors' Response: Thanks for your suggestion. We clarified these questions in the main text. (*page 7-8, the first paragraph of RESULTS*)

Modification: A total of 76 patients who underwent EP from January 2016 to September 2018 were enrolled in the study, 23 of whom were randomly chosen by the surgeons for the novel EP, and the rest underwent the conventional EP.

Discussion

12) "Thus, for a long time, open or minimally invasive surgeries, such as

pancreaticoduodenectomy, have been regarded as the only removal strategy for PAs” Reference.

Authors’ Response: Thanks for your reminder. Reference was included in the text. (*page 9, line 7*)

13) “The drawbacks of these invasive surgeries are obvious”

Thanks for your reminder. References were included in the text. (*page 9, line 9*)

14) “Postoperative adverse events, which occur in around 29% patients,”
Include the reference.

Authors’ Response: Thanks for your reminder. References were included in the text. (*page 9, paragraph 4, line 1-2*)

15) “Accordingly, the adverse event rates of the novel method were significantly lower than those of previous studies” What previous studies?
Include references. They may even be obvious to you, but not to your readers.
Do not be rude.

Authors’ Response: Thanks for your reminder. References were included in the text. (*page 9, paragraph 2, line 5*)

16) “In light of these results” This is a scientific article, please do not bring popular forms of language.

Authors’ Response: Thanks for your suggestion. We modified this phrase to express it more scientifically. (*page 11, line 26*)

Modification: Based on these results,

17) “Hemospray, a hemostatic powder that can rapidly solidify and form an adhesive layer on contact with weak bases, such as water and blood.” I suggest substantiating with the reference: PMID: 31803822

Authors’ Response: Thanks for your reminder. The recommended paper is really a good review on the introduction of Hemospray. Thus, it was cited in the text. (*page 12, paragraph 2, line 4*)

18) “Hemospray is not commercially available in China now, but considering its efficacy, we still look forward to testing it in our novel EP procedure in the future.” Although there is no hemospray in china, is there an article in the literature relating its use and comparing it with glue? Make that clear in your article. With cyanoacrylate, there will be no comparison as it is an injectable method and not a surface method.

Authors’ Response: Thanks for your suggestion. After a thorough search in several databases, we did not find a study compared Hemospray with fibrin glue, but we do think it would be an interesting topic to study on. This was clarified in the text as following. (*page 12, paragraph 2*)

Modification: Another commonly used endoscopic hemostasis method is hemostatic powder, such as Hemospray, a mineral blend powder that can rapidly solidify and form an adhesive layer on contact with weak bases, such as water and blood^[56]. Several studies have shown that Hemospray was efficient in treating GI tract bleeding endoscopically ^[57-61]. EP was recommended as a favorable Hemospray indication^[59]. Although no comparative studies are looking at the efficacy and safety of Hemospray and fibrin glue, both of these treatments are believed to be efficient in treating GI tract bleeding.

19) “In conclusion, the novel method for endoscopic papillectomy is a

potentially safe and effective treatment for reducing postoperative adverse events. It isolates the contact between bile and pancreatic juice with a bile stent, protects the wound surface with metal clips and fibrin glue, and can improve the postoperative condition of patients. Due to the limitations of this study, further research is necessary to verify the claims.” Once again, in your conclusion, you “affirm” what cannot be affirmed and end by saying that you need more studies. I repeat: The conclusion answers your objective and that's it. You cannot say that it is a safe method because your study is retrospective, with selection bias, not randomized, with group location bias. His study "suggests", never claims.

Authors' Response: Thanks for your suggestion. Based on your comments, we modified the conclusion in a more scientific and rigorous way. (*page 12, paragraph 3*)

Modification: Compared with conventional EP, the novel method can reduce postoperative adverse events and improve the postoperative condition of patients. The novel EP achieves its benefits by isolating the contact between bile and pancreatic juice with a bile stent and protecting the wound surface with metal clips and fibrin glue.

Final considerations

In video 1, at 01:52, data appears in the lower-left corner.

Authors' Response: Thanks for your kind suggestion. We found the data was not fully covered at 01:52 of Video 2, so we concealed that part and reuploaded the videos.

- The Article has several grammatical and spelling errors. The English Certificate is BEFORE the author's review. Resubmit for further review and

provide the new certificate.

Authors' Response: Thanks for your suggestion. The manuscript was re-edited by AJE and the new certificate was resubmitted.

Thank you again for helping us improve this manuscript.

Best regards,

Enqiang Linghu