

Response Letter

Dear Editor:

Thank you for giving us an opportunity to revise this manuscript (58390). Reviewer comments and your comments are all valuable and very helpful for revising and improving our paper. We have considered these comments carefully during the revision. A point-to-point response to reviewer's and yours comments is listed below. Relevant changes have been made to the manuscript accordingly, and have been highlighted in yellow. These changes will not influence the content and framework of the paper. We appreciate for the editors and reviewers' warm work earnestly. And we hope the revised version of the manuscript will meet with approval.

Once again, thank you very much for your comments and suggestions.

We look forward to hearing from you soon.

Sincerely yours,

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Replies to editor and reviewers

Title: Endoscopic gastric fenestration of debriding pancreatic walled-off necrosis: a pilot study

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Manuscript No: 58390

Replies to reviewers

Reviewer #1:

1. The text and the tables differ on how long after pancreatitis the procedure was done. Text says 4 weeks but table says sometimes up to 3.5 months. The 17 months I assume is a typo error. Please clarify

Response: It is really true as reviewer suggested that the text and the tables differ on the time interval between pancreatitis onset and endoscopic procedures. In fact, we meant to say, "Endoscopic procedures were all performed > 4 weeks after NP onset". We are very sorry for our incorrect writing. We have revised the text.

As to case 3, the "17 months" in table 1 is indeed true and accurate, rather than a typo error. The patient suffered from necrotizing pancreatitis 17 months before EGF, followed by WON formation. WON was asymptomatic under conservative management for the initial 1 year, but gradually enlarged and caused abdominal distension. Endoscopic drainage was proposed 6 months before EGF, while a fistula was revealed in the stomach that indicated spontaneous rupture of WON into the stomach. Abdominal distension was relieved, and no further intervention was performed at that time. However, the WON re-expanded after transiently declined, and the patient suffered from intracystic infection and hemorrhage 19 days prior to EGF. Intracystic hemorrhage was successfully controlled by emergency intravascular

embolization, while the infection persisted and indicated refractoriness to carbapenem antibiotics. Finally, EGF was performed 17 months after necrotizing pancreatitis onset. Considering the Reviewer's suggestion, we add more details about case 3 in Results/ Baseline characteristics section.

Special thanks to you for your suggestion.

2. What does EUS guided expanded fenestration mean? Please clarify

Response: Fenestration procedure was divided into initial fenestration by ESD approach and expanded fenestration. In the first successful case of EGF (Case 2), initial fenestration area of the stomach by ESD was large (Figure 2E), and expanded fenestration was performed within the initial ESD wound (Figure 2G). As experience of the technique was gained, we found it was unnecessary to resect such a large area of gastric mucosa by ESD during initial fenestration. The initial fenestration area by ESD was narrowed gradually (Figure 2I), while expanded fenestration area was enlarged up to 2.5–3 cm (Figure 2J) with greater precision under EUS guidance and with respect to spatial orientations of WON, rather than blindly expanded, thus avoiding intra-abdominal extravasation of gastric juice.

Special thanks to you for your suggestion.

3. In the table: Why patients 4 and 5 did not have a nasocystic tube placed? And why were they fasting only for 1 day? Why did patients 1-3 fast for longer time? (7 days)

Response: Postoperative treatments were still being developed in this initial case series. Case 1 who failed EGF fasted for 1 wk postoperatively to avoid metal clips shedding and postoperative perforation. For Case 2 and 3, the diameter of fenestration fistula was beyond the caliber of LAMS (up to 1.5-2cm), but we knew little about the healing of fistula at that moment. A nasocystic tube was placed to avoid complete healing of the fenestration fistula and poor drainage of the WON. Meanwhile, both patients fasted for 1

wk until postoperative endoscopy showed surprising self-healing of fenestration fistula, as well as necrotic tissue attachment at the fistula that prevented food from entering the WON. For Case 4 and 5, fenestration fistula was expanded up to 2.5–3 cm to ensure adequate drainage, so a nasocystic tube was no longer necessary. Meanwhile, we tried to restore diet 1 d after EGF, according to the initial experience of EGF and previous experience of endoscopic LAMS drainage. Both patients had no discomfort after eating, so we initially suggested that the diet could be restored as soon as possible if no complications were seen after EGF. Considering the Reviewer's suggestion, we add the details above in **Results and Discussion** sections. Special thanks to you for your suggestion.

4. Although the technique obviates the need for a LAMS, the total cost of the technique reported in the manuscript seem to be inaccurate. The patients need to stay in the hospital for too long (8–36 days) and they need TPN. Also, all the patients underwent subsequent CT scans during their stay after the EGF. All these aspects of the technique add up to the overall cost of it. I am concerned about the very likely possibility that the authors are underestimating the cost of the technique when they state the cost was \$2139.00. That may be the cost of the procedure only, but this technique is generates many more extra costs that the regular LAMS technique does not.

Response: It is really true as reviewer suggested that \$2139.00 was the cost of EGF procedure only, as mentioned in the text and tables. Total costs should include costs for the procedure, postprocedural hospitalisation, readmissions, pharmacy, anaesthesia, radiology, and laboratory and other support. Considering the Reviewer's suggestion, we add the overall cost of hospitalization and follow-up in the revised manuscript. However, the following points need to be considered.

(1) It should be noted that as a preliminary study, we arranged detailed postoperative examinations and treatments to obtain more postoperative data,

including gastroscopy, necrosectomy and CT scans, which would prolong postoperative hospitalization and overall cost.

(2) Patient 1 and patient 3 received other additional endoscopic interventions along with EGF, and suffered complications not related to EGF, which would overestimate the actual postoperative hospital stay and overall cost of EGF.

(3) In fact, there was virtually no solid necrotic tissue remaining in the WON after EGF, which indicated spontaneous drainage of necrotic tissue through the fenestration fistula, just similar to LAMS. In this study, necrosectomy after EGF was performed mainly to remove the necrotic tissue attached to the fenestration fistula for better evaluation of the healing of the fistula. Therefore, TPN was not required in all patients after EGF.

All these aspects mentioned above add up to the overall cost, but some can be omitted in the future as experience of the technique is gained. We realize that it is inappropriate to compare the cost of EGF and LAMS only based on this study, so we will conduct a prospective study to compare EGF with endoscopic LAMS drainage, which can provide more convincing evidence. Special thanks to you for your suggestion.

5. What is the expanded fenestration with snare the text talks about? Please explain

Response: The gastric muscularis propria and adherent WON capsules were both penetrated during initial fenestration, then the fenestration site was expanded by Dual knife, IT knife II or electric snare. Snare was used to resect large pieces of gastric muscularis propria and WON capsules.

6. The second to last sentence in the section titled: "Endoscopic procedures characteristics" is confusing. Did the authors mean "the area of initial fenestration was EXPANDED rather than "narrowed" gradually? in this sentence?

Response: As mentioned in question 2, initial fenestration area of the stomach

by ESD was quite large in the first success case of EGF. As experience of the technique was gained, we found it was unnecessary to resect such a large area of gastric mucosa by ESD during initial fenestration. The initial fenestration area by ESD was narrowed gradually. Considering the Reviewer's suggestion, we add more details in the revised manuscript.

7. It is not clear how the authors internalized the drain in patient # 1 and how was the recurrent infection after internalization was managed.

Response: In patient 1, the nasocystic tube was cut off in the stomach under endoscope, and the external drainage was reverted to internal drainage¹⁵ d later (Figure 1K, 1L). The patient suffered recurrent infection of WON during initial internal drainage, which fortunately responded well to antimicrobial treatment. Considering the Reviewer's suggestion, we add pictures of internalization in Figure 1 K-L, and more details about internal drainage in the **Results/Postoperative characteristics** section.

8. How many necrosectomies did each patient need to clear the cavity? I am concerned about the fact that the gastric window closed significantly within 1 week. This would preclude further endoscopic necrosectomies if needed. Did the authors have to dilate the opening to perform subsequent necrosectomies?

Response: In our study, one or two sessions of necrosectomy were performed in each patient. During EGF, necrosectomy was performed selectively according to extent of necrosis of WON. There was virtually no solid necrotic tissue remaining in WON in endoscopic and CT monitoring 7 d after EGF, which indicated spontaneous drainage of necrotic tissue through the sufficiently large fenestration fistula. Sometimes, necrotic tissue was seen by postoperative endoscopy attached to the fistula, but it rarely affected drainage of WON. Necrosectomy after EGF was performed mainly to remove the necrotic tissue attached to the fenestration fistula, with the primary purpose of obtaining more postoperative data, such as healing of the fistula. Therefore,

necrosectomy was not required in all patients who underwent EGF, and the number of necrosectomy procedures was determined by the extent of necrosis in WON.

It is really true that the gastric window shows surprising self-healing in postoperative endoscope. However, no dilation of the fistula was needed for subsequent necrosectomies as long as the fenestration area of EGF was large enough. We have since realized that fenestration size may need to fluctuate, depending on the dimensions of WON and the necrotic tissues amassed. That's why we have expanded the fenestration size up to 2.5-3cm in the last 2 cases.

Special thanks to you for your suggestion.

Reviewer #2:

1. Dear authors I want to know why the procedural cost is significantly high in the failed case.

Response: In the failed case, initial fenestration was performed by ESD approach, then nasal-cyst drainage tube was inserted instead due to nonadherence of encapsulated WON to gastric wall. Finally, the incised muscularis propria of stomach was closed by metal clips. It costed more consumables and prolonged operating time during the procedures, so the procedural cost was significantly high. This case indicated the importance of selecting appropriate fenestration sites.

Reviewer #3:

1. My Concerns are Direct endoscopic necrosectomy is not required in all patients of WON and about 20%-90% of patients with WON can be treated by endoscopic drainage alone, with either a plastic stent (PS) or fully covered metallic stent. The success rate of DEN is 90-100% and an average 2-3 sessions of necrosectomy are required. Author should discuss about advantage of this technique.

Response: It is really true as reviewer suggested that DEN is not required in all patients of WON. In our study, one or two sessions of necrosectomy were performed in each patient. During EGF, necrosectomy was performed selectively according to extent of necrosis of WON. There was virtually no solid necrotic tissue remaining in WON in endoscopic an CT monitoring 7 d after EGF, which indicated spontaneous drainage of necrotic tissue through the sufficiently large fenestration fistula. Sometimes, necrotic tissue was seen by postoperative endoscopy attached to the fistula, but it rarely affected drainage of WON. Necrosectomy after EGF was performed mainly to remove the necrotic tissue attached to the fenestration fistula, with the primary purpose of obtaining more postoperative data, such as healing of the fistula. Therefore, necrosectomy was not required in all patients who underwent EGF, and the number of necrosectomy procedures was determined by the extent of necrosis in WON. EGF is performed with expanded fenestrations beyond the caliber of a LAMS (up to 1.5-3 cm), which could ensure effective drainage or subsequent necrosectomy if necessary, and eliminate the need for and consequences of stenting. Considering the Reviewer's suggestion, we discuss more about advantage of this technique in revised manuscript. Special thanks to you for your suggestion.

2. Cost analysis was based on the use of LAMS. However, RECENT studies showed that the plastic stent is as effective as LAMS. The criteria for cost analysis is not clear.

3. Cost of using endoscopy suit and endoscopist fees depends on time of procedure. Cost of LEMS is variable in different country. Please segregate these in cost analysis. The average postoperative hospital stay was 17.8 days (range, 8-36 days), therefore, lost work day due to prolonged hospitalisation should also be considered in cost analysis.

Response: It is really true as reviewer suggested that cost analysis was not clear in the manuscript. The cost mentioned in the text and tables was only the cost of endoscopic procedures. Considering the Reviewer's suggestion, we add the overall cost of hospitalization and follow-up in the revised manuscript, and compare it with cost of endoscopic drainage (both plastic stent and LAMS) reported. However, the following points need to be considered during comparison of cost analysis between EGF and LAMS/plastic stent.

(1) In this study, one or two sessions of necrosectomy were performed in each patient. However, there was virtually no solid necrotic tissue remaining in the WON after EGF, and necrotic tissue attached to the fistula rarely affected drainage of WON. Therefore, necrosectomy was not required in all patients who underwent EGF. In this study, necrosectomy after EGF was performed mainly to remove the necrotic tissue attached to the fistula, with the primary purpose of obtaining more postoperative data, such as healing of the fistula. That might overestimate the overall cost of EGF. Meanwhile, the procedural time of EGF was longer than that of LAMS drainage reported, but it could be limited to 60-90 minutes or less when the technique is matured.

(2) Patient 1 and patient 3 received other additional endoscopic interventions along with EGF, and suffered complications not related to EGF, which would overestimate the actual postoperative hospital stay and overall cost of EGF.

(3) As a preliminary study, we arranged detailed postoperative examinations to obtain more postoperative data, including gastroscopy and CT scans, which would certainly prolong postoperative hospitalization and the overall cost. Some postoperative exams might be omitted in the future as experience of the technique is gained

In fact, we realize that it is inappropriate to compare the cost of EGF and LAMS /plastic stent only based on this small sample, preliminary study. A large sample, prospective study to compare EGF with endoscopic LAMS/plastic stent drainage should be conducted, which can provide more

convincing evidence for cost analysis.

Special thanks to you for your suggestion.

4. Case-3: Comparison of EGF and LAMS is little tricky because of difference in location and other characteristic of two WON.

Response: It is really true as reviewer suggested that it is little tricky to comparison EGF and LAMS in the study. As mentioned in question 2, we realize that it is inappropriate to compare the cost of EGF and LAMS only based on this small sample, preliminary study. A large sample, prospective study to compare EGF with endoscopic LAMS drainage should be conducted, which can provide more convincing evidence for cost analysis.

Special thanks to you for your suggestion.

5. Case-1: Less precise selection of the incision site and direction of dissection were other reasons for failures? [CT scan and EUS picture (Figure 1 e and h)]

Response: The challenge of EGF resides in the gauging of actual adherence and in selecting proper sites for fenestration. In Case 1, the selection of the incision site and direction of dissection were performed in the gastric wall closely connected with WON under EUS guidance with unquestionable preciseness. They were not reasons for failure. EGF failed due to nonadherence of encapsulated WON to gastric wall, which was also confirmed by subsequent EUS and X-ray fluoroscopy.

Reviewer #4:

Major point

1. Was the case 1 really WON? The WON of case 1 seems to be PPC. If so, the case 1 should be removed from this study?

Response: Preoperative CT scan and EUS both showed solid necrotic tissue in

the cyst, which was clear especially in Figure 1-H. It was really WON rather than PPC. Case 1 met the inclusion criteria mentioned in **Methods/Patients selection and evaluation** section. Moreover, the failure of this case prompted further refinement of fenestration site selection and the subsequent successful four cases. Therefore, we consider that case 1 is of great significance to the preliminary study and should not be excluded.

Special thanks to you for your suggestion.

2. If EGF is performed for WON, is necrosectomy absolutely necessary?

Response: In our study, one or two sessions of necrosectomy were performed in each patient. During EGF, necrosectomy was performed selectively according to extent of necrosis of WON. There was virtually no solid necrotic tissue remaining in WON in endoscopic and CT monitoring 7 d after EGF, which indicated spontaneous drainage of necrotic tissue through the sufficiently large fenestration fistula. Sometimes, necrotic tissue was seen by postoperative endoscopy attached to the fistula, but it rarely affected drainage of WON. Necrosectomy after EGF was performed mainly to remove the necrotic tissue attached to the fenestration fistula, with the primary purpose of obtaining more postoperative data, such as healing of the fistula. Therefore, necrosectomy was not required in all patients who underwent EGF, and the number of necrosectomy procedures was determined by the extent of necrosis in WON. Considering the Reviewer's suggestion, we add more discussion of necrosectomy in the revised manuscript.

3. When should the meal started after EGF?

Response: Postoperative treatments were still being developed in this initial case series. The previous 2 patients (Case 2 and 3) fasted for 1 wk after EGF until postoperative endoscopy showed surprising self-healing of fenestration fistula, as well as necrotic tissue attachment at the fistula that prevented food from entering the WON. For Case 4 and 5, we tried to restore diet 1 d after

EGF, according to the initial experience of EGF and previous experience of endoscopic LAMS drainage. Both patients had no discomfort after eating, so we initially suggested that the diet could be restored as soon as possible if no complications were seen after EGF.

Special thanks to you for your suggestion.

4. I think that readers want to know how to determine the fenestration site in detail. Would you please explain that by using figures of CT, MRI, EGD, EUS? The figures should be added to a discussion part (Page 13, Lines 9-18) or Figure 2, and the part (Page 13, Lines 9-18) should be moved to the "Technique procedures" part, if you can.

Response: It is really true as reviewer suggested that we should provide more details about how to determine the fenestration site. We add arrows to show the details in the CT, EGD and EUS figures of fenestration site in Figure 2 A-C in the revised manuscript. The characteristics of suitable fenestration sites was not defined initially, but developed on the basis of initial EGF failure gradually. It may be more appropriate to put this part in the discussion section in this preliminary study. However, we can add more details of initial criteria for fenestration site selection in "Technique procedures" part. Meanwhile, we intend to conduct a large sample, prospective study to compare EGF with endoscopic LAMS drainage, and the selection standards of fenestration sites should be placed in the "Technique procedures" that time. Special thanks to you for your suggestion.

5. In the suitable fenestration sites, ulceration of gastric mucosa was raised. Could the EGF been performed at the site near the gastric ulcer?

Response: In this study, gastric ulcer is usually caused by the compression and invasion of WON with close contact with stomach wall, and even the formation of a fistula could be shown in severe cases. There is usually the closest connection between the gastric wall and WON at the site near the

gastric ulcer. We consider EGF could be performed at this site, but it is necessary to pay more attention to bleeding control due to intense inflammation and rich blood supply.

6. If the patient 1 could be removed and the explanation about the suitable fenestration sites is moved to the "Methods" section, the discussion part become shorter. Therefore, the consideration about the difference between EGF and LAMS should be more discussed referencing past reports about LAMS.

Response: As mentioned above, we consider the patient 1 should not be excluded from this study and the characteristics of suitable fenestration sites might be more appropriate to be put in the discussion section. But it is really true as reviewer suggested that the consideration about the difference between EGF and LAMS should be more discussed referencing past reports about LAMS. We have added it in the revised manuscript. Special thanks to you for your suggestion.

7. Minor point 1. In page 3, line 2, the word "WON" had not spelled out.

Response: It is really true as reviewer suggested that abbreviations should be fully spelled out when they appear in the text for the first time. We revised this paper throughout. Special thanks to you for your suggestion.

Replies to Editorial Office's comments

1. Author should discuss about advantage of this technique.

Response: It is really true as editor suggested that we should discuss more about advantage of this technique. We have added more discussion of EGF advantage in the "Discussion" section.

2. The authors need to add more details in the “method” section.

Response: It is really true as editor suggested that we should add more details in the "method" section. We have added more details of fenestration site selection and EUS guided expanded fenestration in the "method" section.

3. The questions raised by the reviewers should be answered;

Response: We have made a point-to-point response to the questions raised by the reviewers. Special thanks to you for your suggestion.

4. I found the language classification was grade C. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Response: The revised manuscript was copyedited by a professional English language editing company. The English Language Certificate was provided.

5. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Original Figures were provided using PPT to ensure that they can be reprocessed by the editor.

6. I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

Response: The “article highlights” section was provided at the end of the main text according to the Guidelines and Requirements for Manuscript Revision.