

Point-by-point responses

Manuscript No.: **63816**

Journal name: **World Journal of Hepatology**

Manuscript type: **Retrospective study**

Manuscript title: **Fatal arterial hemorrhage after pancreaticoduodenectomy: How do we simultaneously accomplish complete hemostasis and hepatic arterial flow?**

Thank you for your valuable suggestions.

According to reviewers' comments, we revised our initial manuscript.

Please review our revised manuscript.

We prepared **Marked revised manuscript** and **Clear version**.

In the marked version (Marked revised manuscript), additional mentions and deleted sentences are shown **in Red with or without strikethrough**.

Also, this summary of responses (**Point-by-point responses**) was separately made.

English language editing

The entirety of our manuscript has been fully checked by English language consultant. Manuscript (Main body, figure legends and tables) has been already checked by English consultant (edanz editing, Identification code: J2101-153481-Hori).

I attached a Certificate issued by English consultant, with this letter.

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Certificate of Editing

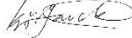
Edited provisional title
Fatal arterial hemorrhage after pancreaticoduodenectomy: How do we simultaneously accomplish complete hemostasis and hepatic arterial flow?

Client name and institution
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To Reviewer #1

Thank you for your valuable evaluations.

According to your comments, we revised our initial manuscript.

Please evaluate our revised manuscript.

1. The importance of this research for fatal hemorrhage after PD

‘Well written manuscript describing 16 patients with fatal GI bleeding in 14-year-old experience of PD surgery. Authors confirmed the need of a customized treatment in such rare but life-threatening complication. Endovascular treatments should be the first-line approach even if several questions emerged. Embolization is very

effective in stopping the hemorrhage but the risk of liver ischemia is considerable. Use of covered stent may be a good option in order to stop the bleeding and preserve blood flow. Patients with worse clinical conditions at PD surgery had worse results after EVT.'

Thank you for your positive evaluation.

2. The first line in the treatment, and decisional chart for journal readers

'These are my suggestions. Which is your first line in the treatment of fatal bleeding after PD; in other words, can you better describe your decisional chart in order to understand the cases in which one approach is preferred over the other one?'

Thank you for your valuable suggestions.

At first, actual therapeutic strategies for our patients who caused arterial hemorrhage after PD were summarized in Figure 7.

According to your suggestion, we added new figure (Figure 7) in the revised manuscript, as an actual treatment flowchart.

Next, we added the mention for our current therapeutic strategy, based on our own experiences which were presented here. We currently have an institutional therapeutic strategy for arterial hemorrhage after PD: (i) CT angiography is performed if general condition is stable, (ii) Diagnostic angiography is immediately performed even in a suspicious patient, and (iii) Covered stent is subsequently placed at the culprit artery as the first line

treatment.

According to your suggestion, we added the mentions for current institutional therapeutic strategy, as ‘Actual therapeutic strategies for our patients who caused arterial hemorrhage after PD were summarized in Figure 7. We currently have an institutional therapeutic strategy for arterial hemorrhage after PD based on our own experiences: (i) CT angiography is performed if general condition is stable, (ii) Diagnostic angiography is immediately performed even in a suspicious patient, and (iii) Covered stent is subsequently placed at the culprit artery as the first line treatment.’ (Page 17 line 1-6, in the Marked revised manuscript).

3. Technical and material details of balloon catheter and covered stent, and type of anesthesia

‘Please discuss the rationale of use a balloon expandable graft over self expandable. Please discuss the technical data of endo approach: sizing and length of balloon (more longer may be related to higher risk of collateral coverage and onset of liver ischemia), the arterial access, type of anesthesia’

Thank you for your valuable suggestions.

Regarding as preliminary dilation by balloon catheter, dilatation was performed based on not size/length but intracatheter pressure. Since stent-graft placement may technically failed due to tortuosity, variation, stenosis, vasospasm or thrombosis, preliminary dilatation by balloon catheter is

indispensable even for self-expandable covered stent. Actual reasons for failed or incomplete EVT in our institution were summarized in **Table 3**.

According to your suggestion, we clearly mentioned these points in the revised manuscript, as 'The target artery was dilated by a balloon catheter (Graftmaster; Abbott Laboratories, Chicago, IL, USA). Balloon catheter pressures was increased in manner of 2 atm per 5 seconds, and the maximum of intracatheter pressure was 15 atm (1520 kPa).' (Page 7 line 25-28, in the Marked revised manuscript), and as 'Stent-graft placement may fail for anatomical reasons (e.g., tortuosity or variation) [13,17,40,59,84,86] or because of catheter-induced vasospasm or spontaneous thrombosis within the aneurysmal wall [17,87-89]. Actual reasons for failed or incomplete EVT in our institution were summarized in Table 3. Since stent-graft placement may technically failed due to tortuosity, variation, stenosis, vasospasm or thrombosis at the culprit artery [13,17,40,59,84,8-89], preliminary dilatation by balloon catheter is indispensable even for self-expandable covered stent.' (Page 15 line 21-28, in the Marked revised manuscript).

Regarding as placement of covered stent, the size and length of covered stent was carefully decided on a case-by-case basis, based on angiographic findings after balloon dilation.'

According to your suggestion, we clearly mentioned these points in the revised manuscript, as 'A covered stent (Graftmaster; Abbott Laboratories), not a bare stent, was placed at the culprit artery. The size and length of covered stent was carefully decided on a case-by-case basis, based on angiographic findings after balloon dilation.' (Page 7 line 28-page 8 line

2, in the Marked revised manuscript).

Regarding as anesthesia, stent-graft placements were generally completed under local anesthesia.

According to your suggestion, mention for type of anesthesia was added in the revised manuscript, as 'In general, procedures of stent-graft placement were performed under local anesthesia.' (Page 7 line 24-25, in the Marked revised manuscript).

4. Medications after treatments

'Which is your post-operative medical protocol (heparin, single-dual antiplatelets), even after discharge?'

Thank you for your valuable suggestions.

Antiplatelet and/or anticoagulation agents were summarized in **Table 3**. Agent types and numbers are also mentioned in **Table 3**.

These patients were all continuously received medication even after hospital discharge.

According to your suggestion, we mentioned these point in the revised manuscript, as 'Antiplatelet and/or anticoagulation agents were administered to five (31.3%) patients (Table 3), and these five patients continuously received medications even after discharge from our hospital.' (Page 10 line 2-4, in the Marked revised manuscript).

5. Concerns exist on use of stent graft in the infected field

‘Concerns exist on use of covered stent graft in infected field. Did this setting modify your choice of treatment between open vs coils vs stent-graft?’

Thank you for your valuable suggestions.

We also have concern regarding the placement of foreign bodies (*i.e.*, coils and stent-grafts) in the setting of infection or inflammation. Intravascular stent infection can be a devastating complication, but previous documents demonstrated that it is very rare. In fact, previous researchers have used stent-grafts to repair infected pseudoaneurysms. Hence, we also consider that stent-grafts can be placed even in suspicious infectious site.

According to your suggestion, we clearly mentioned these points with related references in the revised manuscript, as ‘Concern exists regarding the placement of foreign bodies (*i.e.*, coils and stent-grafts) in the setting of infection or inflammation [40]. Intravascular stent infection can be a devastating complication, but it is very rare [40,64-66]. In fact, stent-grafts have been used to repair infected pseudoaneurysms [67,68]. Though pancreatic juice-related localized infection may associate with pseudoaneurysm and arterial wall erosion [2,6,16,17,22,24,29,39,44,51], we consider that stent-grafts can be placed even in suspicious infectious site.’ (Page 13 line 7-14, in the Marked revised manuscript).

6. Study design

‘The main limit of this study is the small cohort of patients.’

Thank you for your valuable suggestions.

This study was designed as a retrospective study in a single institution. Potential limitations due to bias and a small sample size are inherent to this type of study.

According to your suggestion, we clearly mentioned these points in the revised manuscript, as ‘We acknowledge that this study has several limitations. The main limitation is that this was a retrospective study with a small number of patients from a single center. Of course, we have demonstrated our individual-tailored approach. Potential limitations due to bias and a small sample size are inherent to this type of study. This represents our experience in a single institution and our views may be affected by various biases. Hence, we understand that our conclusions must be drawn with extreme caution.’ (Page 16 line 20-26, in the Marked revised manuscript).

7. Case reports and series for TAE or stent-graft placement

‘A table of available cases in literature on use of covered stent vs embolization may be useful to understand the effectiveness of such approaches.’

Thank you for your valuable suggestions.

Case report and series have described for TAE in quoted documents (Ref# 19,23,30,32,33,69,70,78,79). Also, case report and series have described for stent-graft placement in quoted documents (Ref#

13,16,36,38,85). However, these researchers didn't compare results of TAE and stent-graft placement. Therefore, we separately quoted there case reports and series, only for each advantages and disadvantages.

This point was described, as 'Notably, TAE is occasionally associated with serious hepatic complications caused by hepatic ischemia [1,16,23,30,32,33,69,70]. The liver has many potential collateral pathways that communicate with the adjacent arterial system [16,19,23,29,78,79], and a sudden complete block of HA flow immediately after surgery may induce an ischemic insult to the liver parenchyma [16,29,78,79].' (Page 14 line 15-19, in the Marked revised manuscript) and 'Transcatheter placement of a covered stent may be of value in maintaining the patency of adjacent arteries, and stent-graft placement is an ideal technique to preserve HA flow [1,6,13,16,17,21,27-31,40,54,61,63,80-82]. If necessary, a second overlapping stent-graft can be implanted [40,83].' (Page 15 line 1-5, in the Marked revised manuscript).

8. Deletion of references

'I think too much references are reported. Please consider to choice only the most significant.'

Thank you for your valuable suggestions.

According to your suggestion, the number of the references are reduced in the revised manuscript.

9. Tables and Figures

‘Table OK Figure: OK’

Thank you for your positive evaluation.

To Reviewer #2

Thank you for your valuable evaluations.

According to your comments, we revised our initial manuscript.

Please evaluate our revised manuscript.

1. Covered stent statement and surgical arterioportal shunting

‘This manuscript concerns a very important subject. The authors put forward the use of "covered stent placement" in all cases when possible and the results in terms of mortality seems quite good. Moreover, they describe a technique of arterioportal shunting to limit liver ischemia in case of impossibility to preserve arterial liver blood supply.’

Thank you for your positive evaluation.

2. Shortened discussion section

‘Perhaps, the "discussion chapter" could be shorter but all things

which enter into account in the management of this extremely serious complication are described and well developed.'

Thank you for your valuable suggestion.

According to your suggestion, we deleted one paragraph in the Discussion section and references in the revised manuscript (Page 16 line 12-18, in the Marked revised manuscript).