ANSWERING REVIEWERS

December 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7507-brief articles.doc).

Title: Simplified fistula dilation technique and modified stent deployment maneuver for EUS-guided hepaticogastrostomy

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer #1

A failure of an internal drainage using ERCP technique sometimes requires an external drainage such as PTBD or a surgical procedure, these techniques are considered as more invasive. Thus the construction of internal drainage using EUS and EMS is feasible. Moreover, the concept of the authors' one-step insertion without using several times guidewire manipulations is considered to shorten procedure periods, and seems to be easy to success. In this meaning, the main concept of the authors' article is understandable as case reports. However, some major deficiencies are seen as a report as Phase I/II study. Study design and criteria are poor and rack of acceptable evaluations. These are described below:

1. **Authors have to set or describe the primary endpoint, the secondly endpoint and discontinuance**

criteria. The aim of authors' study was unclear and unknown whether which feasibility authors tried to prove in Phase I study.

Our primary endpoints of Phase I study were to evaluate the success rate, procedural time and adverse event rates of our modified and simplified methods in EUS-HGS. One of the most important and difficult things in EUS-HGS is to dilate the fistula. Therefore, we calculated the sample size based on the successful fistula dilation rate and then the calculated sample size was used as the stopping rule for patient recruitment in phase I study. However, there was no standardized or reference value of success rate, procedural time and adverse events of EUS-HGS. Therefore, it was impossible to define the discontinuance criteria in phase I study.

2. **Authors should describe adverse events along with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Did authors not know this evaluation method? Authors concluded that the adverse events (%) did not reach significance, however, the massive hemorrhage was clearly a Grade 3 adverse event only observed in Modified method group. Thus, authors have to show other all adverse events' Grades. It is an ordinary method for the clinical trial.**

   The reviewer recommended that the severity of adverse events should be described according to the CTCAE. However, the CTCAE is not appropriate for the description of EUS-HGS related adverse events. Proximal migration is one of the most serious adverse events in EUS-HGS. But, there was no comment about this in CTCAE. Moreover, there is no significant difference in serious adverse events between modified and conventional method even if we regard the bleeding as grade 3 (4% vs. 0%, $P > 0.99$). Therefore, it seems that application of CTCAE in this study is not appropriate. Instead, we adopted "A lexicon for endoscopic adverse events: report of an ASGE workshop" for the explanation of adverse events (Gastrointest Endosc 2010;71:446-454).

3. **Does it have any meaning to compare Overall survival in Table 3 even though the patients' disease and staging were not standardized? Benign disease was also included!**

   The reason we mentioned about overall survival is because we wanted to clarify that there were no procedure-related mortality. We think it is not necessary to standardize the patients according to the disease and staging since this study was aimed to validate the efficacy and safety of the new EUS-HGS technique.

4. **Authors have to describe inclusion criteria (indication) more specifically. How many patients with high grade hilar biliary stricture, failed guidewire manipulation or PTBD refusal? These technical difficulties must influence the results.**

To minimize the difference of technical difficulties in EUS-HGS, we compared the modified method and conventional method by matched case-control study (etiology of biliary obstruction and age). As described in **Table 3**, there were 15 patients with perihilar obstruction each in modified method group and in conventional method group without statistical difference ($p > 0.99$). There was no significant difference in the number of surgically altered anatomy between the two groups (6/23 vs. 6/23, $p > 0.99$). There were 9 and 7 patients respectively who underwent EUS-HGS due to failed guidewire manipulation during ERCP or EUS-guided rendezvous ($p = 0.54$). There was no patient who underwent EUS-HGS due to PTBD refusal. We mentioned about this in **Table 3** as follows:

Table 3 Age and etiology matched case-control results

	Modified method (n = 23)	Conventional method (n = 23)	*P*-value
Mean age (± SD), years	62.9 ± 14.6	64.1 ± 12.8	0.88
Male, no. (%)	17 (74)	12 (52)	0.13
Etiology of bile duct obstruction			> 0.99
Benign	1	1	
Perihilar lesion	15	15	
Periampullary lesion	5	5	
Peribiliary or metastatic lymph node	2	2	
Surgically altered anatomy	6	6	> 0.99
Failed guidewire manipulation during ERCP or EUS-guided rendezvous	9	7	0.54
Technical success rate, no. (%)*	22 (96)	21 (91)	> 0.99
Functional success rate, no. (%)†	20 (91)	16 (76)	0.24
Use of needle knife, no. (%)	1 (4)	1 (4)	> 0.99
Procedure time, mean (± SD), min	15.3 ± 5.2	22.3 ± 6.0	< 0.001
Median stent patency (95% CI), d	216 (73-359)	129 (64-194)	0.73
Total adverse event (%)	2 (9)	8 (35)	0.07

Early, no. (%)	0	6 (26)‡	0.02
Late, no. (%)	2 (9)	2 (9)§	> 0.99
Overall survival (95% CI), mo	7.5 (5.6-9.4)	4.3 (1.8-6.8)	0.27

5. **Total/direct bilirubin should be described before and after the procedure. The efficiency criteria of the drainage authors defined was only 75% decrease of the bilirubin. Is it defined as effective if bilirubin decreased to 0.8mg/dl after the procedure from 1.1mg/dl? Needless to say, direct bilirubin is important. Success rate was defined by this definition, thus this point should not be overlooked.**

   The decrement of total bilirubin level is dependent on the value of pretreatment bilirubin and level of biliary obstruction. If the initial bilirubin is less than or equal to 10 mg/dL, it takes 3 weeks to achieve adequate normalization of serum bilirubin. However, if the initial bilirubin level is more than 10 mg/dL, it takes more than 6 weeks to achieve adequate normalization of serum bilirubin. (Cancer 2008;112:2417-2423). The mean level of total bilirubin was 10.3 mg/dL in this study. Therefore, we defined the functional success as a decrease of bilirubin to < 75% of the pretreatment value within the first month like our previous publications. (Am J Gastroenterol 2009;104:2168-2174, Gastrointest Endosc 2010;72:1279-1284, Gastroinest Endosc 2010;71:413-419, Gastrointest Endosc 2011;74:1276-1284, Gastrointest Endosc 2013;78:91-101).

6. **Authors have to describe whether no patients receive the second treatments such as pancreatodudodenctomy or gastrojejunostomy.**

   There were no patients who received the second treatment. According to Reviewer #1's comments, we mentioned about this in **RESULTS** section as follows:

   "Serum total bilirubin decreased significantly within 1 month after EUS-HGS (10.3 ± 9.4 to 3.7 ± 5.1 mg/dL, P < 0.001). During mean follow-up period of 5.2 months, no patients received the second treatments such as pancreaticoduodenectomy or gastrojejunostomy after EUS-HGS."

Reviewer #2

EUS-guided biliary drainage (EUS-BD) is an emerging alternative to PTBD or surgery after failed ERCP.

You performed modified method," the role of a 4mm balloon dilation catheter with a stainless steel stylet and modified stent deployment maneuver with an 8mm fully covered metal stent with dual flap".

You compared with the conventional EUS-HGS technique. Authors concluded the procedural time was shorter and early adverse events were less frequent with our simplified and modified technique.

But you experienced 2 late adverse events, gastric migration of the stent and bleeding from left hepatic pseudoaneurysm.

I ask some questions.

1. Please explain much detail mechanism of left hepatic artery pseudoaneurysm.

We described about left hepatic artery pseudoaneurysm in detail.

"The patient with pseudoaneurysm was presented as hematemesis 8 months after EUS-HGS. There was huge fresh blood clot attached to stent in endoscopic finding (Figure 4A). Since pseudoaneurysm from left hepatic artery was noted around the proximal end of hepaticogastrostomy stent in CT (Figure 4B), hemostasis was achieved by urgent embolization of the feeding vessel from the left hepatic artery (Figure 4C)."

Figure 4 Development of pseudoaneurysm as a late adverse event after EUS-guided hepaticogastrostomy. A: There was huge fresh blood clot attached to stent in endoscopic finding. B and C: Since pseudoaneurysm from left hepatic artery was noted in CT and angiography, hemostasis was achieved by embolization of the feeding vessel from the left hepatic artery.

We also explained the mechanism of pseudoaneurysm in **DISCUSSION** section as follows:

After intrahepatic biliary decompression, the relatively large diameter of FCSEMS with the anchoring flap may erode the intrahepatic bile duct, resulting in a left hepatic artery pseudoaneurysm. The presence of pseudoaneurysm at the tip of the stent may suggest the possibility of its development due to compression of the arterial wall by the metal stent. Further larger studies of metal stents with a modified proximal tip (e.g., an uncovered portion without flared ends or a flap or with a smaller diameter) may be needed to address this issue.

2. From the point of early complication, conventional method is much higher (26%) compared with modified technique (0%). Please tell me the reason why conventional method have high rate complication.

As the Reviewer #2 has pointed out, the early adverse events were more frequent in conventional method compared with modified method. It seems that the shortening of procedural time by using simplified one-stage fistula dilation with 4 mm balloon catheter may be associated with less frequent early adverse events. Because the dilation force of a balloon catheter is radial, the separation of tissue

planes would be less compared with repeated graded tract dilation with bougie catheter. Our modified stent deployment maneuver also prevents the separation of tissue planes. Furthermore, since the modified stent deployment maneuver guided by fluoroscopy and EUS has an advantage in stabilizing the position/attachment of the scope to the hepaticogastrostomy site, the chance of proximal or distal migration of the stent would be reduced. We already mentioned about this in **DISCUSSION** section.

Reviewer #3

The authors are congratulated for performing a retrospective case comparison for performing hgs with a novel anti-migratory stent. Several minor comments

1) I don't understand how the sample size was calculated. If this was just a retrospective review than no sample size calculations Is required. If you are performing a prospective study then sample size should be calculated. But it wasn't clear if you are assuming difference or no difference between the two groups as calculation is quite different

Since the phase I study was a prospective study comparing the technical success of simplified fistula dilation method with conventional method, we calculated the sample size. The sample size was used as the stopping rule for patients recruitment who receive modified HGS method in phase I study. We already described about this in "**Statistical analysis**" section.

2) what is the mean fu time of the patients?

The mean follow-up time was 5.2 ±3.6 months. We described the mean follow-up time in **RESULTS** section as follows:

"During mean follow-up period of 5.2 months, no patients received the second treatments such as pancreaticoduodenectomy or gastrojejunostomy after EUS-HGS."

3) although the authors claim that the difference between the 2 groups of patients is due to the technical difference, this can still be due to difference in the experience of the endoscopist In performing the procedure. The authors should mention this in the discussion.

We totally agree with your opinion. So, we described about this as the limitation of this study. However, the patients who received conventional method were collected after about 60 cases of EUS-BD were performed. Our previous two studies showed a comparable procedural time and no reduction in the procedural time, despite possible technical proficiency with time trends (Gastrointest Endosc 2010;71:413-419, Am J Gastroenterol 2009;104:2168-2174). Therefore, the effect of the difference in the technical proficiency of the operator on procedural time trends is likely minimal.

4) there was a significant in migration rate between the two groups, is this due to the design of the stent? Perhaps the authors can Hv more discussion in his issue

In our previous study comparing anchoring flap vs. flared end fully covered metal stent for benign biliary stricture, the antimigration effect was superior in anchoring flap than in flared end (Gastrointest Endosc 2011;73:64-70). However, as we mentioned in other studies (Am J Gastroenterol 2009;104:2168-2174, Gastrointest Endosc 2010;71:413-419), the fully covered metal stent with a flared end may be enough preventing migration for very tight biliary strictures. Initially, there was a waist of metal stent at the site of hepaticogastrostomy site. Therefore, it seems that there are no differences in early stent migration between the two types of FCSEMS. The technical difference of fistula dilation and stent deployment maneuver may be more important factors for the early migration of stent. However, if the hepaticogastrostomy site is dilated by the expansion of metal stent, there might be a difference of stent migration between anchoring flap and flared end as benign biliary strictures. Since the follow-up duration was not enough in this study, there were no significant difference of late adverse events such as stent migration between two groups. Further long-term studies will be required. We mentioned about this in **DISCUSSION** section as follows:

"The difference of stent design might have affected the postprocedural stent migration. With regard to the antimigration effect of FCSEMS for benign biliary stricture, the anchoring flap design was superior to the flared end design [17]. However, the FCSEMS with a flared end may be enough preventing migration for very tight biliary stricture [6, 7]. There is a waist in the middle of the stent at the site of hepaticogastrostomy site when the metal stent is initially inserted. Therefore, it seems that the difference of stent design would not be a significant factor affecting early stent migration in EUS-HGS. However, if the hepaticogastrostomy site is dilated by the expansion of metal stent, there could be a difference of stent migration between anchoring flap and flared end like benign biliary strictures. Since the follow-up period was not enough in this study, there was no significant difference of late stent migration between two groups. In order to verify about this issue, further long-term studies will be required."

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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