

Dear Editor

We are most grateful to you and the reviewers for the helpful comments on our manuscript entitled “Urgent endoscopic ultrasound-guided choledochoduodenostomy for acute obstructive suppurative cholangitis-induced sepsis” (ESPS manuscript number: 23694). We have accommodated all comments and suggestions in the revised version of our paper.

A point-by-point reply to these comments is attached.

We have corrected a misspelled word in the title ‘choledocoduodenostomy’ to ‘choledochoduodenostomy’. And one of the co-author’s name was corrected from ‘Miayata’ to ‘Miyata’.

This manuscript has not been published in or submitted to any other journals. All authors contributed significantly to the work and are in agreement with the content of the manuscript. All authors also agree to the conditions outlined in the copyright assignment form.

We hope that our revised manuscript meets the requirements for publication in *World Journal of Gastroenterology*.

Yours sincerely,

Masayuki KITANO, Kosuke MINAGA,

Department of Gastroenterology and Hepatology

Kinki University Faculty of Medicine, Osaka-Sayama, Japan

Based on the comments from the reviewer, we have made changes of the manuscript, which are detailed below. Please note that reviewer comments are indicated in italics. Our replies are in bold black font. Texts that are referred to in our replies are indicated by grey highlighting.

Reviewer’s code: 00503857

COMMENTS TO AUTHORS

The authors described 3 cases of acute obstructive suppurative cholangitis which were successfully managed with EUS-CDS. The manuscript is nicely written and the topic is interesting. This manuscript can be accepted for publication in WJG after minor revision. Some minor suggestions are described below.

1. *The authors should describe how to manage patient’s airway while performing*

EUS-CDS, especially in the first patient, whose vital signs were not stable. Was the first patient intubated while receiving EUS-CDS? Some might argue against endoscopic method for treating unstable patients.

A1. We appreciate your important comments. In our institution, EUS-guided biliary drainage was performed in more than 150 cases under deep sedation using intravenous midazolam and propofol. The level of sedation was titrated to optimize the tolerance to the procedure without compromising respiration using a bispectral index monitor and a pulse oximetry. Patients were continuously monitored during the procedure with an automated noninvasive blood pressure device, and on electrocardiogram tracing. As you pointed out, the vital signs of the first patient were unstable due to sepsis. Performing EUS-CDS procedure under intubation may be preferable in such a case. In this patient, the respiratory function was relatively stable (SpO₂; 100%, room air). At the previous hospital, ERCP was performed 6 hours before under moderate sedation with midazolam and there were no problems during the ERCP procedure. Therefore, we performed EUS-CDS using a small amount of midazolam without intubation. There was no sedation related problem during the procedure. We have added the following sentences: The procedure was performed without intubation after administration of a small amount of intravenous midazolam. The depth of the patient's sedation was titrated by continuous monitoring with a bispectral index monitor and a pulse oximetry.

2. The authors should describe how to manage CBD stones after insertion of 2 plastic stents. Do you plan to perform EUS-RV or surgery?

A2. Thank you for your constructive comments. In the case 1 and 2, when we suggested options for performing rendezvous technique or surgery to extract CBD stones, the patients and their families did not choose to undergo these procedures because both patients did not have any new symptoms and their AOOSC-induced sepsis had resolved. Therefore, we decided to routinely replace the stent semiannually. We think this management could be acceptable for such elderly patients because patients older than 65 years may be at greater risk of comorbid cardiopulmonary and cerebrovascular diseases, making them unfit to undergo surgery or endoscopic procedure of long duration. We have added the following sentences and three articles describing about these issues as references.

(case report)

Patient 1: When we suggested options for performing rendezvous technique via the CDS fistula or surgery to extract the CBD stones, the patient and her family did not choose to undergo these procedures because she did not have any new symptoms. Therefore, we decided to exchange stents semiannually. During 8 months of follow-up, the patient was free of any symptoms and we exchanged the stents endoscopically 6 months after the initial procedure.

Patient 2: We suggested options for performing rendezvous technique or surgery in the same manner as described in case 1, she did not wish for these invasive procedures. Therefore, we decided to exchange stents semiannually. During 4 months of follow-up, the patient was free of any symptoms.

(discussion) Endoscopic transpapillary biliary stenting remains an effective alternative for patients with stones difficult to manage by conventional endoscopic methods and those who are unfit for surgery or have high surgical risks. There is no standardized time period for routine stent replacement of endoscopic transpapillary biliary stenting. Stent patency rates declined rapidly from 94% at 6 months to 79% at 12 months and 58% at 24 months. Therefore we decided to exchange stents semiannually in case 1 and 2.

Reviewer's code: 00227359

COMMENTS TO AUTHORS

This is a new indication of an emerging endoscopic technique, EUS guided CD. When the ERCP failed in the patients with obstructive jaundice, patients become septic and an urgent biliary decompression becomes inevitable. As another interventional endoscopic technique, EUS guided biliary drainage can be life-saving. Here the authors described three similar cases with acute obstructive cholangitis. It is known that this new procedure is more common for the malignant biliary obstructions. Although the authors claimed that this was the first report on this topic for benign diseases, a recent systematic analysis including 1186 cases of EUS guided biliary drainage reported several benign pathologies. Maybe a second check of the literature can be safer before saying the first report.

A. Thank you for your kind comments. I read a recent systematic analysis including 1186 cases of EUS guided biliary drainage. We suggest that the first means EUS-CDS underwent urgently 'in patients with septic shock' due to benign lesions, but our expressions could lead to misunderstanding. We had deleted the

following sentence in the introduction part: To the best of our knowledge, this is the first report of urgent EUD-CDS performed for AOSC-induced sepsis due to benign lesions.

Reviewer's code: 00183658

COMMENTS TO AUTHORS

This retrospective case series were aimed to describe three cases of successful biliary drainage with recovery from septic shock after urgent endoscopic ultrasound-guided choledocoduodenostomy was performed for acute obstructive suppurative cholangitis due to biliary lithiasis. The title is "Urgent endoscopic ultrasound-guided choledocoduodenostomy for acute obstructive suppurative cholangitis-induced sepsis".

- 1. Several factors influence the outcomes of the study. Some limitations might be occurred.*

A1. Thank you for your helpful comments. We have added the limitations. The limitations of this study were the small number of patients, lack of a control group, and the inclusion of only a single operator at a single tertiary-care referral center.

- 2. This procedure needed an experienced endoscopist and special equipment. It could not apply in the community hospitals.*

A2. Thank you for your constructive comments. We have added the following sentences in the introduction paragraph; All procedures were carried out by a single experienced endoscopist (M.K.) at a tertiary-care referral center. All EUS procedures were performed using a therapeutic linear echoendoscope (GF-UCT260; Olympus Medical Systems, Tokyo, Japan) with carbon dioxide insufflation. And we have added the following sentence in the discussion part; The limitations of this study were the small number of patients, lack of a control group, and the inclusion of only a single operator at a single tertiary-care referral center.

- 3. Please discuss this issue "Why didn't the physicians routinely perform EUS-CDS procedure?"*

A3. We appreciate your kind comments. ERCP with transpapillary biliary stenting has been well established technique for providing biliary decompression in patients with bile duct obstruction. However, we believe that EUS-CDS in the near future

will be a suited salvage to patients whom ERCP cannot be performed. There are some problems to be solved. One is that bile leak is a concern during EUS-guided biliary interventions and most series have demonstrated that biliary leakage into the peritoneal space is the most dreaded complications of EUS-CDS. Therefore, the development of new comfortable device dedicated for EUS-CDS are needed. If the new device will be available, EUD-CDS will become easier and safer in the future. We have added the following sentences in the discussion part: Although endoscopic retrograde biliary stenting has been well-established technique for providing biliary decompression in patients with bile duct obstruction, we believe that EUS-CDS will be a suited salvage to patients whom ERCP cannot be performed. There are still some problems to be solved. One is that bile leak is a concern during EUS-guided biliary interventions and previous studies have demonstrated that biliary leakage into the peritoneal space is the most common complications of EUS-guided biliary drainage. Therefore, the development of new comfortable stenting device that facilitates simultaneous puncture/dilation is needed. If it becomes available, EUD-CDS will become easier and safer in the future.

4. *Please also add the clinical application in the discussion section.*

A4. Thank you for your kind advice. We suggest that elderly patients with AOSC due to biliary lithiasis after failed ERCP could be a preferred candidate for EUS-CDS because endoscopic procedure of long duration may lead to causing increase in morbidity and mortality. We have added the following sentences in the discussion part: We suggest that patients with AOSC due to biliary lithiasis after failed ERCP could be preferred candidates for EUS-CDS because endoscopic procedure of long duration may lead to causing increase in morbidity and mortality especially in elderly patients with AOSC-induced sepsis.

Reviewer's code: 00045997

COMMENTS TO AUTHORS

In this case report, Minaga and colleagues assessed techniques and efficacy of urgent endoscopic ultrasound-guided choledocoduodenostomy for acute obstructive suppurative cholangitis-induced sepsis. They showed their excellent outcomes in three cases as well as a short review. The findings of this retrospective study are of considerable interest. I have no serious criticism except minor issues which are shown below. In case 1, a covered metallic stent and a nasobiliary tube were replaced. In case

2, only a covered metallic stent was replaced. In case 3, plastic stent was replaced. Why did these procedural variances happen? Please describe concisely. In case 1 and 2, authors did not retrieve stones but exchanged stents to keep the fistula patent, while they removed stones in case 3. Please describe shortly the reason of the different therapeutic decision.

Thank you for your insightful comments. We placed a covered metallic stent and a nasobiliary tube in case 1 because the previous report recommended the use of a nasobiliary drain to decrease the pressure in the punctured bile duct. In case 2, we attempted to place the nasobiliary tube but the guidewire slipped. In case 3, the patient had DIC, so we hesitated to dilate the fistula using a balloon catheter to insert metal stent although a recent systematic analysis showed that the adverse events were lower using the metal stents than plastic stents. The reason of the different therapeutic decisions was as follows. In case 1 and 2, we suggested options for performing rendezvous technique or surgery, they did not wish for these invasive procedure. Therefore, we decided to exchange stents semiannually although it is technically possible to retrieve stones endoscopically. We have added the following sentences: The drainage of the CBD can be achieved by two different types of stents, metal and plastic. In case 1 and 2, covered metallic stents were deployed and in case 3, plastic stent was deployed. According to a recent systematic analysis, the post-procedure adverse events were lower in the metallic stents although there were no differences in technical and functional success rates between metallic and plastic stents. In case 3, the patient had increased risk of bleeding due to DIC. Concerning this risk, we avoided to insert a metallic stent for it needs fistula dilation using a balloon catheter. We placed a nasobiliary tube through the metallic stent in case 1 because the previous report recommended the use of a nasobiliary drain for 48 hours to decrease the pressure in the punctured bile duct. In case 2, we attempted to place the nasobiliary tube but the guidewire slipped and failed to place it.

Reviewer's code: 02455208

COMMENTS TO AUTHORS

Interesting and well-written article. However it's about a very demanding technique and only small numbers have been published. Concerning the implementation in benign diseases in particular, there is very little, if no, documentation. Are there any issues with this fistula in the long run in a young, healthy patient with choledocholithiasis? More

cases and long-term follow up is a necessity. Still, it's a leap forward.

A. We appreciate your interest to our manuscript. As you mentioned, we are not sure whether there are some issues with this fistula in the long run in a young patient with choledocholithiasis as we followed-up patients only for short term. In this report, all 3 patients were elderly (older than 75), therefore we suggest that the preferred candidates for this technique are elderly patients with AOSC after failed ERCP. We have added the following sentences: We suggest that patients with AOSC due to biliary lithiasis after failed ERCP could be preferred candidates for EUS-CDS because endoscopic procedure of long duration may lead to causing increase in morbidity and mortality especially in elderly patients with AOSC-induced sepsis. And, in the discussion part we have added the following sentence: Further 'long-term' studies with a larger cohort are needed to prove the efficacy and safety of this technique.

Reviewer's code: 01467363

COMMENTS TO AUTHORS

Title and running title: appropriate to define the content of the manuscript. Key words: 5, defining the content of the paper. Abstract: is appropriate, not structured, 137 words. Core tip: 100 words, appropriate to define the content. Case presentations: 841 words, presentation of three life endangered elderly patients (83, 85, 80 years old), diagnostic and therapeutic procedures are described in detail, including laboratory data and imaging methods. The therapeutic procedures are illustrated with 3 figures (abc/ab/ab). Discussion: 464 words, although brief, the discussion is relevant, presented are the data of studies/informations concerning this problem. This treatment method was first reported in 2001 by Giovannini et al., and since then it has been increasingly performed as an alternative in patients with malignant biliary obstruction for failed ERCP. The indication for benign biliary disease has not been established. In the three presented cases successful urgent EUS-CDS for benign disease - choledocholithiasis was performed. Conclusions: last paragraph, short, 50 words, with a clear message for further studies and larger cohorts of patients to prove the efficacy and safety of this therapeutic method. References: 11, relevant, from Endoscopy 2001 to Gastrointest Endosc 2015, influential journals in the field of endoscopy. Conflict of interest: all authors declare no conflicts-of-interest. Ethics of the study: the study was approved by the Institutional Review Board of Kinki University Faculty of Medicine. Informed consent: all study participants, or their legal guardian, provided informed written

consent prior to study enrollment

A. We appreciate your interest to our manuscript.