

Format for ANSWERING REVIEWERS

January 14, 2017



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 31181-answering reviews.doc).

Title: Efficacy and safety of limited endoscopic sphincterotomy before self-expandable metal stent insertion for malignant biliary obstruction

Author: Hyeong Seok Nam, Dae Hwan Kang, Hyung Wook Kim, Cheol Woong Choi, Su Bum Park, Su Jin Kim, Dae Gon Ryu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 31181

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

We appreciate the comments and suggestions provided by the reviewers and the editor, and the opportunity provided to improve our manuscript. We have carefully revised the manuscript and all the changes in the revised manuscript are in blue-color font. Point-by-point responses to the comments are listed below.

Reviewer's code: 00070271

COMMENTS TO AUTHORS

Dear authors: I have reviewed your manuscript. Your results and statistical analysis are well done. In general I found very interesting your work. However some corrections need to be done: First of all, this is not a clinical trial study, as you have classified it at the very top. This is a retrospective study as you mention also in some parts of the manuscript. The journal demands to add acknowledgments, conclusion and comments. Remember to use square brackets in every citation.

Abstract If you read the guidelines for the manuscript the aim must not have more than 20 words; please modify it. You have to adhere to the word count thresholds; methods must not have less than 80 words and the conclusion no more than 26 words; also the keywords are less than the required.

Reply : Thank you for your comments. We have re-classified this study as retrospective. We have revised the abstract to satisfy the word requirements of the journal. We have also added additional

sections as advised by you.

Introduction No comments.

Materials and methods The number of patients included has to be mentioned in your results, not in this section. Same observation for the number of patients classified according to the type of cancer. The inclusion criteria needs to be more specific. Mention the main clinical findings; also mention the main laboratory parameters which were used. Clarify if all the patients had all the radiological studies mentioned, or if radiologic studies were practiced according to particular characteristics of each patient and to the evidence of a malignant biliary obstruction. Clarify how bleeding was intended to be detected.

Reply : We removed the sentence concerning the number of patients from the section on materials and methods. The inclusion criteria have been explicitly stated in this section. We have also included the presence of principal clinical findings such as painless jaundice and/or pruritus and the main laboratory parameters. We have provided clear details about the radiological studies that were used.

Endoscopy was performed to evaluate ES-related-bleeding on the day following stent placement. Bleeding was recognized based on patient's history (melena or hematemesis) and the identification of decreased hemoglobin level following the procedure. Mild bleeding was defined as hemoglobin drop within 2 g/dL, with no necessity for blood transfusion.

Results You describe that you included patients with cholangitis pre-procedure (68 patients) while in your exclusion criteria you mention patients with severe cholangitis with or without septic shock. Which was the parameter to separate the patients included with cholangitis from the ones excluded with severe cholangitis. Do this on your material and methods to avoid confusion. The term endoscopic retrograde biliary drainage does not appear on the text while its abbreviation (ERBD) is used on the tables please do this correction. Percutaneous transhepatic biliary drainage does not have an abbreviation in the text while the abbreviation (PTBD) is used on the tables. The only factor statistically significant related to the complications rate that you mention (number of SEMs initially deployed) is not well described. How many patients with one SEMs deployed developed PEP or bleeding. Same observation with the patients with tow SEMs deployed.

Reply : We have provided a detailed description of the definition of cholangitis and severe cholangitis according to updated Tokyo guidelines (TG13) for diagnosis and severity grading of acute cholangitis in material and methods to avoid any confusion. The expansions of the abbreviations used in the table (ERBD, PTBD) have been provided as footnotes to the table. We have also provided data regarding the number of patients that developed PEP or bleeding based on the number of SEMs deployed. We also added a table to provide information about the occurrence of complications based on patient characteristics (table 6).

Discussion Your discussion is well founded. Although, aspects like the number of stents initially

deployed are not discussed. Also at table 2 your analysis reveals p values < to 0.05 between cancer groups related to the number of SEMs initially deployed, the stent complication and the patency, which need to be included in this section of the manuscript. Also why is the number of attempts of cannulation not analyzed, considering it a risk factor for PEP. Tables: Table 2 title should change to Characteristics and complications according to cancer type. Please make the corrections requested. Thank you

Reply : We attempted to explain the relation of the number of stents deployed initially and its relation to the incidence of complications as follows: Bilateral stent placements for Bismuth type II to IV hilar cholangiocarcinoma are also very complicated and result in increased endoscopic manipulations^[32]. The higher incidence of post-ERCP complications in patients who had two SEMs (bilateral stents) placed could be related to these reasons.

Although our analysis (Table 2) reveals p values < to 0.05, the relationship between cancer groups and the number of SEMs initially deployed did not appear very meaningful to us. The difference may be due to the inclusion of patients with cholangiocarcinoma. This group includes Klatskin tumors (esp. Bismuth type II to IV hilar cholangiocarcinoma) that often require two SEMs (bilateral stents) to be placed initially. Therefore, the difference in outcome may be related more to the anatomical characteristics of the disease. Correspondingly, the p value is 0.161 in the case of stent complications.

We refrained from commenting on patency in this section since we had not analyzed it in detail. Our aim was to focus on the technical aspects of limited ES before SEMs insertion and its complications. The analysis of patency is beyond the scope of this study.

In non-pancreaticobiliary cancers such as ampullary cancer, stomach cancer, duodenal cancer PTBD is the preferred method of reintervention. We assumed that pancreatic cancer, with relatively short survival, is more aggressive than other conditions, and may have a relatively lesser need for further procedures. We analyzed the characteristics according to the incidence of complications and found that the number of attempts for cannulation did not affect PEP rates (Table 6).

We changed the title of Table 2 to "Characteristics and complications according to cancer type".

Reviewer's code: 03025323

COMMENTS TO AUTHORS

This paper is mentioned about the efficacy and safety of limited ES accompanying SEMs placement for malignant biliary obstruction. Though it is a retrospective study, I think that it is clinically useful. But I think that there are some problems in this article.

Minor revisions

If there is no difference between with limited ES and without, I think we may not perform limited ES. Because there are some complications, and it cost more than without ES. In case of high risk of PEP we should perform limited ES. It has been mentioned by literature (No. 17). How do you

think about it? In case of hilar biliary stricture, are there any cases, which were placed across the papilla? Were only distal biliary stricture cases placed across the papilla? The author should add about the above-mentioned.

Reply : Our aim in this study was to identify the efficacy and safety of ES. This study showed that limited ES is not associated with any significant increase in complications. ES on its own may allow for easier stent placement and reduce resistance to biliary instrumentation and facilitate stent exchange. However, we agree with your opinion and further studies with control groups are required to provide an objective comparative analysis of the benefits of ES.

Previous studies demonstrated that ES may be unnecessary in pancreatic cancers with obstruction of the main pancreatic duct. However, it is possible that ES may be advantageous in selected cases, depending on pancreatic duct status, stent diameter, stent type (especially fully covered SEMs) or ampulla size as we described in our discussion. Further studies are needed to confirm the role of ES in this group of patients.

We have provided additional descriptions regarding the location of the inserted stent according to the stricture site. In the case of hilar biliary strictures, SEMs was placed above the sphincter of Oddi. Placement was across the papilla in distal biliary strictures alone.

Reviewer's code: 03262085

COMMENTS TO AUTHORS

In this study, treatment outcomes of the group of patients who received limited endoscopic sphincterotomy for malignant biliary obstruction are demonstrated by disease group, by site of stenosis, and by stent type. The performance of the treatment as a whole is comparable to those already reported. However, the novel point or element compared to existing reports is not clear. Whether NSAIDs or protease inhibitors were used for preventing post-ERCP pancreatitis should be mentioned. Was the cannulation method for the biliary tract, either the wire-guided cannulation or the conventional cannulation with contrast medium? If both were used, do you have any strategy to use one or the other?

Reply : In clinical practice, many endoscopists routinely perform ES before SEMs placement, including limited ES in cases with malignant biliary obstruction. However, there is inadequate data regarding the associated complications. We showed that limited ES does not increase complications. Our data demonstrates relatively low complication rates compared to published literature, and provides justification to the performance of limited ES prior to SEMs placement in these patients. Previous reports did not clarify the results of ES based on its extent, and may have overestimated the risk of limited ES. Our study is the first one to provide objective data on the basic usefulness and complications of limited ES before SEMs insertion for malignant biliary obstruction.

We have added information regarding our measures to prevent post-ERCP pancreatitis as advised by you. While NSAIDs or other drugs were not used, nafamostat mesilate (20 mg) was

administered to all patients for preventing post-ERCP pancreatitis. We detailed the cannulation method in the study protocol; the wire-guided cannulation technique was attempted first. If biliary cannulation was not achieved within 10 min, then the conventional contrast-assisted cannulation technique was applied.

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

Sincerely yours,

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