Format for ANSWERING REVIEWERS

May 8, 2015

Dear Editor,

Thank you for your consideration of our manuscript "Early EUS in acute biliary pancreatitis: a prospective pilot study".

Please find enclosed the edited manuscript in Word format (file name: 17468-review.doc).

Title: Early EUS in acute biliary pancreatitis: a prospective pilot study

Author: Andrea Anderloni, MD PhD, Marianna Galeazzi MD, Marco Ballarè MD, Michela Pagliarulo MD, Marco Orsello MD, Mario Del Piano MD, Alessandro Repici MD.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17468

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

1 Format has been updated

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

Comment 1:

Please provide language a certificate letter from a professional English language editing company (Classification of the manuscript language quality evaluation is B).

Reply:

We asked to Boldface Editors (an international editorial service) to revise our manuscript. Please find attached the certificate letter.

Boldface Editors is an International Editorial Service established in 1987 to assist non-English speaking research scientists prepare their manuscripts for publication consideration in high-impact biomedical journals worldwide.

Comment 2:

The title must be informative, specific, and brief (Title should be no more than 10~12 words/60 bytes. Please revise it). Words should be chosen carefully for retrieval purposes. All nonfunctional words should be deleted, such as 'the', 'studies on', 'observations of', and 'roles of', *etc*

Reply:

We have edited the title reducing the words number to 10: "Early EUS in acute biliary pancreatitis: a prospective pilot study"

Comment 3:

Author names should be given first, then the complete name of institution, city, province and postcode. Please add.

Reply:

This change has been provided

Comment 4:
An informative, structured abstract of no less than 336 words should accompany each original article
Reply:
The abstract was created as requested (476 words)

Comment 5:
Clinical Trial Registration Number requested
Reply:
We have added the Clinical Trial Registration Number: NCT02430285

Comment 6:
Core tip (no more than 100 words)
Reply:
We have added the core tip (84 words)

Comment 7:
All figures, tables and legends should not be in the main text. They should be put at the end of this paper.
Reply:
We have put all figures, tables and legend at the end of the paper as requested.

Comment 8:
Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.
Reply:
We have added Pub Med citation numbers and DOI citation as requested.

Comment 9:
References: no less than 30 references.
Reply:
We have corrected the reference section accordingly.

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

Reviewers' comments (Reviewed by 00057328):

Summary: in this manuscript, the value of endoscopic ultrasound for detecting common bile duct stones and thus selecting patients for subsequent ERCP was explored in 71 patients with acute biliary pancreatitis. % patients with bile duct stones at endoscopic ultrasound was higher in patients with moderate or high a priori risk of bile duct stones. Comments: 1. It is not entirely clear on what criteria patients were subdivided as low, intermediate or high probability of bile duct stones. 2. All patients were apparently having predicted mild pancreatitis. Were patients with predicted severe pancreatitis excluded? 3. Some important information is missing in Table 1 concerning clinical data: especially CRP

(>150 considered severe pancreatitis), and duration of pancreatitis pain before the hospital admission. 4. It is not clear how long after hospital admission, endoscopic ultrasound and (if done) ERCP were performed. 5. The data from this work appear in contrast with previous studies which indicated that clinical data such as bili , bile duct dilatation with ultrasound etc had low positive and negative predictive values for presence/absence of bile duct stones (see Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. van Santvoort HC et al.Endoscopy. 2011 Jan;43(1):8-13. doi: 10.1055/s-0030-1255866.). This should be discussed in the discussion section. 6. Most bile duct stones in case of biliary pancreatitis will spontaneously pass, also related to the fact that gallstones are generally small in case of biliary pancreatitis. Therefore, it is not clear that ERCP would change cause of the disease, even in case of documented bile duct stones with EUS.

Comment 1.

It is not entirely clear on what criteria patients were subdivided as low, intermediate or high probability of bile duct stones.

Reply:

We thank the reviewer for this comment and we have edited the manuscript to make it clearer (See page 6)

Diagnosis of CBDS is generally based on clinical signs and symptoms, serum markers of cholestasis, imaging tests (abdominal US). Different prognostic scores, formulas, and algorithms have been proposed to help predict the probability of choledocholithiasis.

In our study we've decided to classified patient as low, intermediate or high probability of CBDS presence on the basis of the literature [Barkun AL et al. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. Ann Surg 1994; 220(1): 32-39. / F. Tse, J. S. Et al. The elective evaluation of patients with suspected choledocholithiasis undergoing laparoscopic cholecystectomy. Gastrointest Endosc 2004; 60(3): 437-48./ASGE Standards of Practice Committee. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc 2010; 71(1): 1-9.]

Since our patient were all symptomatic for abdominal pain (inclusion criteria) serum AST and ALT level were indeed elevated in all the patients therefore we have take into account only the following markers:

Bilirubin level (< 2 mg/dL; between 2-4 mg/dL and > 4 mg/dL)

Common bile duct dilation at transabdominal US (CBD diameter normal vs dilated),

as previously described in another paper written by our group [A. Anderloni et al. Prospective evaluation of early endoscopic ultrasonography for triage test in suspected choledocholithiasis; results from a large single centre series. Dig Liver Dis. 2014 Apr;46(4):335-9.]

We therefore have considered patient at low risk if bilirubin level was < 2 mg/dL and CBD not dilated, high risk if bilirubin level was more than 4 or more than 2 with concomitant CBD dilation, intermediate risk any of the other combination.

See page 6 in the manuscript.

Comment 2.

All patients were apparently having predicted mild pancreatitis. Were patients with predicted severe pancreatitis excluded?

Reply:

We thank the reviewer for the thoughtful comment. Indeed, in our manuscript we have excluded patient with predicted severe pancreatitis (this is now clearly mentioned in the exclusion criteria (see page 7).

Comment 3.

Some important information is missing in Table 1 concerning clinical data: especially CRP (>150 considered severe pancreatitis), and duration of pancreatitis pain before the hospital admission.

Reply:

We thank the reviewer for this comment.

Acute pancreatitis was established by the presence of two of the three following criteria: (i) abdominal pain consistent with the disease,(ii) serum amylase and / or lipase greater than three times the upper limit of normal, and / or (iii) characteristic findings from abdominal imaging. Predicted severity of acute pancreatitis was assessed in all patients within 48 hours after the onset of symptoms. Criteria for predicted severe pancreatitis was modified Glasgow score of 3 or higher (an mentioned in the "methods" section, see pag 6). We've chosen the Glasgow System as it is a simple prognostic score that uses age and 7 laboratory values (serum albumin, Arterial pO2, Serum calcium, blood glucose, serum LDH, serum urea nitrogen, WBC) collected during the first 48 hours following admission for pancreatitis. PCR values were collected for each patient included in the study anyway (data not shown) but we thought this parameter was not fundamental for the purpose of this study.

As far as the duration of pancreatitis pain before the hospital admission is concerned, this was less than 24 h for each patient.

Comment 4.

It is not clear how long after hospital admission, endoscopic ultrasound and (if done) ERCP were performed.

Reply:

All enrolled patients underwent EUS within 48 h of their admission (see the "methods" section, page 7). ERCP was performed immediately after EUS only in those cases with proven CBD stones or sludge. Patients defined negative for EUS were followed for a 6-month period with telephone calls at 1, 3, and 6 months after EUS.

Comment 5.

The data from this work appear in contrast with previous studies which indicated that clinical data such as bili , bile duct dilatation with ultrasound etc had low positive and negative predictive values for presence/absence of bile duct stones (see Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. van Santvoort HC et al.Endoscopy. 2011 Jan;43(1):8-13. doi: 10.1055/s-0030-1255866.). This should be discussed in the discussion section.

Reply:

We thank the Reviewer for underlining this important point.

Indeed we think the results of our study highlight the unreliability of commonly used clinical, biochemical and radiological predictors for CBD stones presence, confirming the conclusions of the previous studies. This point was addressed in the "Discussion" section (see page 14) "Our data confirm that the commonly used clinical, biochemical and radiological predictors of the presence of choledocholithiasis are unreliable for predicting the presence of CBD stones, with the exception of CBD dilatation at transabdominal US. All the other predictors, including bilirubin, AST, ALT, GGT, alkaline phosphatase, and cholecystolithiasis at transabdominal US were not significantly associated with CBD stones."

In particular, it is worth noting that 20% of patients stratified in the low-risk group according to clinical parameters were found to have CBD stones by EUS (that means low NPV of the commonly used predictors of CBD stones presence), thus undergoing ERCP and avoiding the risk of further pancreatic

damage. By contrast, in 50% of patients allocated in the high-risk group based on clinical parameters, CBD stones were not found by EUS (that means very low PPV of the commonly used predictors of CBD stones presence), thus avoiding unnecessary ERCP.

Our results are therefore not in contrast with the literature and in particular with the paper written by van Santvoort HC et al. Moreover they strongly confirm the unreliability of commonly used clinical, biochemical and radiological predictors for CBD stones presence.

Comment 6:

Most bile duct stones in case of biliary pancreatitis will spontaneously pass, also related to the fact that gallstones are generally small in case of biliary pancreatitis. Therefore, it is not clear that ERCP would change cause of the disease, even in case of documented bile duct stones with EUS.

Reply:

We strongly agree with the reviewer. Nevertheless this point was beyond the aim of our study and the role and timing of endoscopy in the setting of acute biliary pancreatitis (ABP) is still being debated by the literature.

Biliary pancreatitis results from the migration of a gallstone to the common bile duct (CBD) with impaction or temporary obstruction of the major duodenal papilla. Most ABP attacks are not severe, are self-limiting, and improve with conservative management [Frey CF et al.The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. Pancreas 2006; 33(4): 336-344.].

Spontaneous passage of CBD stones in the duodenum has been described in up to 50% of cases of ABP [Frossard JL et al. Choledocholithiasis: A prospective study of spontaneous common bile duct stone migration. Gastrointest Endosc 2000; 51(2): 175-179./Cavdar F et al. Controversial issues in biliary pancreatitis: When should we perform MRCP and ERCP? Pancreatology 2014; 14(5): 411-414.].

However, conservative management of these patients is associated with a biliary complication rate of up to 20%. In such cases, ERCP is delayed and must be performed under possibly more difficult conditions, thus increasing the failure rate [Neoptolemos JP et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988; 2(8618): 979-983./Fölsch UR et al. The German Study Group on Acute Biliary Pancreatitis. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. N Engl J Med 1997; 336(4): 237-242.].

Moreover, without definitive treatment, the risk of a recurrent attack within the next several months is about 30–50% [DeIorio AV Jr et al. Acute biliary pancreatitis: The roles of laparoscopic cholecystectomy and endoscopic retrograde cholangiopancreatography. Surg Endosc 1995; 9(4): 392-396./Kuo VC, Tarnasky PR. Endoscopic management of acute biliary pancreatitis. Gastrointest Endosc Clin N Am 2013; 23(4): 749-768.].

Even after a mild attack, cholecystectomy and/or biliary sphincterotomy should be considered within weeks. In a large retrospective study, Nguyen et al.[Nguyen GC et al. Early cholecystectomy and ERCP are associated with reduced readmissions for acute biliary pancreatitis: A nationwide, population-based study. Gastrointest Endosc 2012; 75(1): 47-55.] demonstrated that hospital readmission rates for ABP within 12 months were significantly reduced with cholecystectomy (14.0% vs. 5.6%) or ERCP (13.1% vs. 5.1%).

4 References and typesetting were corrected

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

Sincerely yours,

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