

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5692-edited manuscript).

Title: Early precut sphincterotomy and the risk of endoscopic retrograde cholangiopancreatography related complications- an updated meta-analysis

Name of Journal: World Journal of Gastrointestinal Endoscopy

ESPS Manuscript NO: 5692

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

(1) In reference to this comment:

A well done review and analysis of available studies. I feel that the authors should emphasize the fact that precut should be done only for therapeutic ERCP, as is the case for nearly all ERCPs. Any complication occurring in patients undergoing diagnostic cholangiopancreatography would be unacceptable. They could also briefly give the factors associated with higher complications following ERCP in general to make the review complete.

Certain patients are considered to be high-risk for development of PEP. In a meta-analysis by Macsi et al, patients with suspected sphincter of Oddi dysfunction (RR 4.09, 95% CI 3.37-4.96; $P < 0.001$), female gender (RR 2.23, 95% CI 1.75-2.84; $P < 0.001$), and those with a previous history of pancreatitis (RR 2.46, 95% CI 1.93-3.12; $P < 0.001$); additional procedure-related risk factors for PEP were pancreatic sphincterotomy (RR 2.71, 95% CI 2.02-3.63; $P < 0.001$) and pancreatic injection (RR 2.2, 95% CI 1.6-3.01; $P < 0.001$). We have added this information in the article.

Masci E, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy* 2003; 35: 830-834

(2) In reference to this comment:

This paper confirms that precut sphincterotomy is not more harmful than persistent attempts of cannulation of the papilla in terms of pancreatitis and other complications. The meta-analysis is based on not very recent papers but it is well done and the inclusion criteria are correct and well defined. ? The main issue to me is that it is not well clarified if the patients with "late precut in persistent attempts" (as written in Table 3) are those considered in the group of precut patients or are a category apart. Actually, these patients (with late precut) could have a worse outcome than those who had an early precut, by adding the traumatism of several attempts to that of precut. The issue may be confusing and should be better detailed. If possible a comparison should be made between early and late precut?

We did a sub-analysis as requested by the reviewer. Of the seven studies, Tang SJ et al study did not include late precut in their analysis. The study by Cennamo V et al study included early and late pre-cut subgroup and sub-analysis did not show any difference ($P=0.25$). The study

by DeWeerth A et al included both early and late pre-cut, but the authors that there was no difference in the complications. However, no data was available to do sub-analysis. The other two studies by Manes G et al and Swan M et al included patients in early and late pre-cut, but the authors mentioned that subgroup analysis did not showed any statistical difference in the PEP complication rates.

(3) In reference to this comment:

As the authors outline, the techniques employed for cannulation and precut were different in the included studies (needle-knife, standard freehand precut from the papillary orifice, fistulotomy starting above the orifice). The possible significance of this in altering or modifying the outcomes should be emphasized, considering that different techniques may offer different incidence of complications.?

We have made the changes as suggested by including a discussion about them.

(4) In reference to this comment:

In one study among those considered, prophylactic pancreatic stents were used. This introduces a significant variable and I would eliminate this study from the meta-analysis.

In the study by Swan M et al, pancreatic duct (PD) stents were used. There was no significant difference in the use of PD stents between the 2 randomized groups, 15 of 34 (44%) in the standard cannulation arm and 23 of 39 (59%) in the NKS arm. Similarly, there was no statistical difference in the use of PD stents in the standard cannulation group vs. those in the standard cannulation arm who required crossover to NKS, 5 of 12 (41%) vs. 10 of 22 (45%). Multivariate analysis of risk factors for PEP showed that PD stent insertion did not affect the results (OR=1.67; 95% CI-0.47-5.90; P-0.43). Since the study is a well done RCT and given the lack of RCTs on this topic, excluding this study would make the meta-analysis less up to date with the literature.

(5) In reference to this comment:

The running title "Pancreatitis and pre-cut sphincterotomy" could be better modified in "ERCP complications and pre-cut sphincterotomy"? at page 5, 3rd line from below: "decrease" should be substituted by "increase"? at page 6, line 5 it is written "Subsequent to this publication, another RCT has been published". There is no mention of the results of this publication, as can be expected by the reader. Moreover, several numbers of references in the text should be positioned before and not after the marks. ? at page 7, 8th line from below "(M.S)We" should be written "(M.S.): We"

Changes have been made as requested by the reviewer.

(4) Core tip summary and comments have been added

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Gastrointestinal Endoscopy.

Sincerely yours,

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