Author's response to reviews

Title: Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis

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Author's response to reviews: see over
Dear Claudia Browning:

We thank you and the reviewers for giving us the opportunity to revise this manuscript. We have carefully reviewed the comments raised by the reviewers and the changes have been made accordingly in the revised manuscript. The following are the point-by-point response to the reviewer’s comments.

Reviewer: Takeshi Tsujino

Major Compulsory Revisions

1. The results of the present study do not seem very impressive. None of the well-designed RCTs have shown that corticosteroid does not prevent pancreatitis after ERCP (eg, De Palma GD et al. Am J Gastroenterol 1999, Sherman S et al. Gastrointest Endosc 2003), while only one small-scale RCT (Kwanngern K et al. J Med Assoc Thai 2005) found its efficacy; on the contrary, gabexate, of which the same leading author has recently reported a meta-analysis, was found to be effective for the prophylaxis of post-ERCP pancreatitis in the well-designed multicenter RCT (Cavallini et al. N Engl J Med 1996; 335:919-23). I do understand that a meta-analysis definitely provides solid evidence, but I wonder why the authors conducted this study.

   The well-designed RCTs certainly provide solid information about effectiveness of drugs. However, there are still some different results from these trials especially that most recent trials usually have different outcomes than previous trials. One example is the effectiveness of gabexate for the prophylaxis of post-ERCP pancreatitis. In 1996, Cavallini et al found that gabexate was effective for the prophylaxis of post-ERCP pancreatitis in the well-designed multicentre RCT. But recent well-designed multicenter RCTs (Andriulli et al Gastrointest Endosc 2007, 65(4):624-632; Manes et al Gastrointest Endosc 2007, 65(7):982-987) found that gabexate could not prevent post-ERCP pancreatitis, which is consistent with the result of our meta-analysis of gabexate for the prophylaxis of post-ERCP pancreatitis. Meta-analysis is a statistical method to combine the results of several studies that address a set of related research hypotheses. Although there were different scales in the RCTs related to corticosteroid prophylactic use for post-ERCP pancreatitis, different outcomes have been observed. Therefore, it would be necessary to perform meta-analysis of these RCTs.

2. In addition, the authors state in Background that the contradictory results of corticosteroid in the prophylaxis of post-ERCP pancreatitis can only be resolved from large prospective RCTs. The US multicenter RCT by Sherman et al. (Sherman S et al. Gastrointest Endosc 2003) is one of the largest studies (n =1,115) on the pharmacological prevention of post-ERCP pancreatitis. Do they consider that the power of this RCT is inadequate to draw conclusions?

   We have modified the sentence in Background section. It is not our intention to mean that the well-designed multicenter RCT by Sherman et al. (Sherman S et al. Gastrointest Endosc 2003) has no power to draw conclusion. It certainly provides solid evidence. At the same time, meta-analysis will also provide useful information from multiple RCTs.
3. I am afraid, but I have to say that Discussion needs to be improved further. 1) In the 1st paragraph in Discussion, the authors have described repeatedly what was written in Background. 2) In the 2nd paragraph, they discuss on the retrospective study by Weiner et al. and the small RCT by Kwanngern et al. Unfortunately, I consider that these two studies are less important, as compared to well-designed RCTs (eg, Sherman S et al. Gastrointest Endosc 2003). I’d rather the authors discussed these RCTs. 3) Recently, RCTs have had a tendency to be targeted to the patients at high-risk for pancreatitis, the very group of patients who could benefit from pharmacological prevention. This meta-analysis did not address the stratified data, which seems the major limitation of this study.

Both reviewers have concerns regarding the section of Discussion. We have made significant revision of Discussion, such as to discuss the outcomes of different RCTs regarding prophylactic application of corticosteroid for post-ERCP pancreatitis.

Minor Essential Revisions

1. Methods; The authors excluded patients with chronic pancreatitis and pancreatic cancer. However, some RCTs included both or either of these groups of patients (eg, De Palma GD et al. Am J Gastroenterol 1999, Sherman S et al. Gastrointest Endosc 2003).

We have corrected the exclusive criteria in the previous version. Chronic pancreatitis and pancreatic cancer have been included.

2. Results; In order to make the readers understand easily, the authors would express the incidence (percentage) of post-ERCP pancreatitis in the two groups.

The incidence (percentage) of post-ERCP pancreatitis in the two groups has been indicated.

Reviewer: Alberto Mariani

Major Compulsory Revisions

Although data appears to be complete, the manner of presentation makes the manuscript more detailed by a statistical or technical than by a clinical point of view.

The discussion needs a complete rewrite: too much extended the part referred to the first retrospective study; there are many results and few comments.

A better English language is mandatory.

We have considerably modified the manuscript to be detailed by a clinical point of view. The discussion has been rewritten and the manuscript has been discussed and consulted with a Chinese professor at the University of Manitoba, Canada. It is our hope that a better English language can be met.

Minor Essential Revisions

BACKGROUND:

Page 3 line 6: “…… Were still 10% of cases…..” Add a reference.

The reference has been included.
RESULTS:

Combine Table 1 and Table 2.

Comments for table 1:

1. In the first column substitute reference with author and year of publication (i.e. Budzynska, 1997).
2. Keep “setting” as second column
3. Put in the third column quality or Jadad score (i.e. 0-5) reported in your table 2.
4. Put in the fourth column “sample size” data
5. Delete “patient inclusion criteria”. Specify in the methods that 4 out of 7 studies included patients submitted only to diagnostic ERCP and 3 to diagnostic and therapeutic ERCP).
6. Delete “outcomes”. PEP was the common outcome of all the studies. Specify in the methods that in two studies the grade of severity of PEP was not reported or that a severe PEP was reported in five studies.
7. Describe in the methods the allocation concealment judgment and not in the table.
8. Include other three columns (fifth, sixth and seventh column) about type, dosage (mg) and duration (min/h) of corticosteroid administration.
9. Delete table 2 and the last line (from “the quality…. To Table 2) in the Assessment of study quality paragraph (page 4, line 14-15).

We have combined Table 1 and Table 2 and modified Table 1 as suggested by the reviewer.

Comments for Table 3 and 4:

Keep your Table 3 and 4. Change titles, i.e.: Sensitivity analysis of the effect of corticosteroid prophylaxis of post-ERCP pancreatitis in clinical trials.

The titles of Table 3 and Table 4 have been changed according to reviewer’s suggestion.

Comments for Figure 2:
1. Change the title of the figure. Example: Effect of corticosteroids in the prophylaxis of post-ERCP pancreatitis. In the Forest plot (figure 2a) values of relative risk … in the Funnel plot (figure 2B at the place of Figure 3).……

2. Put in the middle of the figure (as shown in your table 4) the terms PEP (delete 01 PEP), severe PEP (delete 02 ..) and post-ERCP hyperamylasemia (delete 03…) to better emphasize them as subtitles of the figure.

3. Delete the two columns on the right of the figure: “weight %” and “OR (fixed) 95% CI”.

4. In the first column, insert “pooled” in place of subtotal (95% CI)” reporting the following numbers: 157/1312 and 142/1320 for corticosteroid and placebo, respectively.

5. Show by small size characters the OR (fixed) and 95% IC values for each of the three sub-categories just on the right of the triangular sign into OR (fixed) column.

6. In the first column delete, for each sub-category, the following three lines: total events …., test for heterogeneity….. and test for overall effect…… Show the results of the test for heterogeneity and overall effect in the text (result section).

7. Into the new figure 2b (in place of your figure 3) it’s better to show data by OR (fixed) against sample size (number; i.e. 10-10000) axis deleting the two diagonal lines.

Comments for Figure 2 have been incorporated in the new Figure 2.

In closing, we would like to thank yourself and reviewers for your insightful comments and suggestions. We hope that with the changes outlined above, this manuscript will be deemed acceptable for publication.

Yours truly

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