Reviewer's report

Title: "Treatment of acute pancreatitis with protease inhibitors: an updated systematic review and meta-analysis."

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Reviewer: Rupjyoti Talukdar

Reviewer's report:

In this meta-analysis, the authors have evaluated the role of protease inhibitors in ameliorating severity of acute pancreatitis. This is an extension of a previous meta-analysis by the same authors from 2006. Results from both the meta-analyses showed lack of any benefit from protease inhibitor. The rationale for use of protease inhibitors have probably stemmed from experimental evidence that there is intra-acinar activation of protease (trypsinogen to trypsin followed by activation of other proenzymes) after an acute insult to the pancreas. Intra-acinar activation of proteases after acute insult to the pancreas occurs very early on in the natural history of the disease; and by the time the patient reaches the hospital these intracellular activities would have already occurred. The morbidity and mortality of the patients is a result of the inflammatory response and local complication resulting from the initial events. Therefore, it is not surprising that protease inhibitors won’t have any plausible role in ameliorating the severity of the disease, except for specific predictable situations like post-ERCP pancreatitis. Nevertheless, this has to be backed by clinical evidence for which trials and meta-analysis (like the current one) becomes important. Even though the study appears sound from a statistical standpoint, the authors need to address certain issues.

General comment:

There is a need for language and grammatical corrections.

Specific comments (Major compulsory revisions):

INTRODUCTION:

1. Please provide some more detail on the previous meta-analysis, for eg. total no. of studies included, sample sizes in the control and intervention groups, study outcomes, etc.

METHODS:

1. How was severity defined? How was the CMR calculated?

2. Why was post-ERCP pancreatitis excluded? Conceptually this is an ideal group where protease inhibitors might have some beneficial role. A subgroup analysis could have addressed this issue.

3. Inclusion criteria were described separately in two places. All of these can be written together.
4. The authors seem to have evaluated too many outcomes. Authors should divide the outcomes into one primary and the other related ones should be described under secondary outcomes. Pain relief and paralytic small bowel obstruction can be removed as outcomes since these do not necessarily depend upon the severity of disease.

5. How was 'other major complications' defined?

6. How was low, moderate and high heterogeneity among the studies defined?

RESULTS:

1. The text in the section of Selection and features of trials may be shortened and only the salient features be written, since the same are expressed in Figure 1 and Table 1.

2. Mention the exact I2 values wherever mild, moderate and high heterogeneity is mentioned.

3. Figure 2: I guess outcome presented in this Forrest plot is mortality. Add this in the legend. What does -.44329 and .443297 indicate? Add the heterogeneity (I2) and the 'p' value in the Forrest plot.

DISCUSSION:

1. The results from the current and the authors’ previous meta-analysis (2004) are similar. Therefore, describe clearly the salient differences between the two studies, and the rationale why this meta-analysis was taken up.

2. The last paragraph in the discussion lacks clarity.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests