

June 18th 2015

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Editors-in-Chief
World Journal of Gastroenterology

Ref.: "Epidural anesthesia improves pancreatic perfusion and decreases the severity of acute pancreatitis"- No. 19273

Dear Editors,

We would like to thank the reviewers for their time reviewing the manuscript and their thoughtful comments. We have revised our manuscript to address reviewers' comments. The changes are highlighted in track changes. Below are specific responses to the reviewers' comments and all changes made to the manuscript.

Reviewers' comments:

Reviewer #1

There are problems to be discussed in this paper

1-small number of patients

We agree with the reviewer in that we did not reach the desired accrual for this study. We mentioned in the limitations of the discussion section on page 15 that the study had been interrupted and enrollment was closed after 49 patients because the recruitment of patients with severe acute pancreatitis in the emergency setting showed to be extremely difficult. Our explanation was that patients randomized for epidural anesthesia had a higher rate of drop out, compared to the standard therapy group. This resulted in uneven study groups, which would then bias our results.

2-there is no confirmation of reduction of ongoing necrosis in EA group

Thank you for this important comment. We determined follow-up in our study as the duration of hospital stay. We showed that length of stay was not statistically different between the two groups, with 26 days in the EA group versus 30 days in the control group. The complications were monitored as clinically indicated and are all cited in the manuscript for the entire length of hospital stay. Patients were discharged when clinically deemed safe. As mentioned in the method section for Co-variables, parameter of clinical severity and complications by repeat imaging studies were collected and reported. Clinical signs of improvement and favorable evolution on imaging were an estimate for regression of necrosis.

3-There are no data about fluid administration on both group. If EA induces hypotension its possible that the EA group received more fluid?

Thank you for this excellent point.

Although our patients were monitored on clinical surgical wards or in the ICU, the exact administered IV fluids were not measured and recorded. Our believe is that the differences were not major; and either way, if the volume in the epidural group had been more important, this fluid overload would have been viewed as a negative clinical outcome (edema), in terms of its effect on overall pulmonary or renal function, or intestinal paresis.

4-The beneficial effect of EA could be related to increased intestinal perfusion and therefore reducing intestinal barrier dysfunction?

Our hypothesis is that the beneficial effect of EA could be related to a better intestinal perfusion as well. This would result in a protection of the intestinal barrier, such as less bacterial translocation etc, and might have contributed to the clinical improvement in our patients. The effect of EA on gut perfusion has been studied and those studies have been mentioned in the manuscript discussion section on page 14, however, our randomized trial was not designed to investigate the effect of EA on intestinal perfusion and its possible complications resulting from acute pancreatitis.

Reviewer #2

1. The title describe well the manuscript 2. The abstract summarized well the manuscript 3. Description of method are clear 4. Results are reported well 5. Discussion is well organized 6. References are well reported 7. Tables and Figures are clear.

We thank the reviewer for these comments.

8. One final word is about the term “severe AP (acute pancreatitis) in this manuscript; 3 lines in the abstract 3 pages, 3 lines in the methods 16 pages, 19 lines in the results 10 pages, 23 lines in the Discussion 14 pages. Authors defined severe AP as a Ranson score ≥ 2 and/or a C-reactive protein (CRP) > 100 mg/L and/or necrosis on CT. This is not correct according to the Atlanta classification as well as the Revised Atlanta classification. So, I would recommend that “severe AP” should be changed to “predicted severe AP”.

We agree with the reviewer and have made the changes on all cited pages in the manuscript, changing severe AP to “predicted severe AP”, according to the Atlanta Classification.

Changes made to the manuscript:

1. The manuscript statements have been added on page 2 of the manuscript.

2. Changes have been made to the abstract on page 4 of the manuscript to fulfil the minimum requirement for word counts.
3. The “comments” section has been added to the manuscript on page 16-17 of the manuscript.
4. The DOI and PMID numbers have been added to the reference list.
5. Figure 1 has been added in word format for editing on page 25 of the manuscript in addition to the Figure 1 in TIF format.
6. The manuscript has been edited by an English language service, without changing the content of the study. The certificate is included in the submission.
7. The manuscript has been subjected to CrossCheck (iThenticate). The report is attached to the submission.
8. The final title has been subjected to Google Scholar. A “screenshot image” is attached with submission. This study has been presented as an abstract at the “Swiss Society of Surgery” Conference in Davos, Switzerland in June 2012.

We would like to thank you for the opportunity to revise our manuscript and look forward to hearing your decision.

Sincerely,

Samira Sadowski and Leo Bühler