

March 23, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:). 1796-EDITED final.docx

Title: Effect of oral mesalamine on inflammatory response in acute uncomplicated diverticulitis.

Authors: Luca Nespoli, MD; Giulia Lo Bianco, MD; Fabio Uggeri, MD, Fabrizio Romano, MD, Angelo Nespoli, MD, Davide Paolo Bernasconi, MSc, Luca Gianotti, MD, ScD.

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 17096

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 reviewers. Below you may find a list of the revisions that were made with point-by-point responses to the comments of the reviewer. Any change in the text has been highlighted in red.
- 3)References and typesetting were corrected
- 4)Language editing was carried out by an expert native English speaker.

Thank you again for considering our manuscript for publication in the World Journal of Gastroenterology.

Sincerely yours,

Luca Nespoli, MD

Response to reviewer 1 (02945445)

1) *It should be mentioned whether IBD patients were excluded.*

IBD patients were excluded from the analysis. We added a statement in this regard in the Materials and Methods section

2) *There are a number of points mentioned in the materials and methods that should be referenced (they are listed, but only later in the text). In particular: the authors mention evidence that relates to high-dose mesalamine administration and recent trials on the use of mesalamine in diverticular disease.*

We added references where needed.

3) *Primary endpoints should instead be successful non-operative treatment (e.g. need for surgery), time to resumption of oral food intake, and time to hospital discharge. This would make more sense based on the author's aims.*

In our retrospective, case-cohort, analysis we focused on the potential impact of mesalamine in affecting the acute inflammatory process in acute uncomplicated diverticulitis. Standing from this perspective, CRP levels have been considered has an ideal endpoint. We agree that, starting from this pilot data, further investigation should aim to evaluated relevant and clinical parameters as primary endpoints, as suggested.

4) *p values should be listed in the results section text.*

P values were added where needed

5) *There is a typo in the discussion. The setence Two four arms open label trials should instead read "Two four-armed open label..."*

We modified the passage in accord with your suggestions.

6) *There are additional limitations that should be included, such as the small number of patients and there may be significant selection bias as the study was not randomized.*

Additional limitations of the study have been added in the discussion section, as suggested.

Response to reviewer 2 (17096)

Methods

1. *Authors have to describe:*

a. *how long was mesalamine treatment during the acute treatment.*

The length of treatment prosecution following hospital discharge was defined for each patient by the attending physician. Our institutional database included only inhospital data, no additional follow-up information was available for the present study.

This has been specified in the Material and Methods section.

b. which antibiotic was administered in the two study groups: was it the same? By which route was administered (intravenously or by oral route?)

In the period of interest, our internal protocol for antibiotic therapy included a combination of quinolones and metronidazole given intravenously to all patients that were not allergic or intolerant. Following your suggestion, this has been specified in the Material and Methods section.

c. whether and how acute diverticulitis resolution was assessed: by abdominal CT scan? On clinical assessment?

Acute diverticulitis resolution was assessed clinically. We have now specified it in the materials and methods section.

2. Have the authors assessed whether mesalamine influence the outcome of those patients? In other words, did the authors find a difference:

a. in diverticulitis recurrence if treated with mesalamine supplementation or not?

b. in controlling chronic abdominal symptoms if treated with mesalamine supplementation or not?

Our retrospective, case-cohort study, evaluated data from an institutional database including only inpatient information. A long-term evaluation of mesalamine administration was not assessed because it was not the aim of this study.

Discussion

3. Authors have to provide further explanation on the mesalamine failure in obtaining pain relief when compared to standard treatment. In particular, this point is quite differing when compared with patients suffering by symptomatic uncomplicated diverticular disease (SUDD), in whom mesalamine seems more effective than placebo in controlling abdominal pain (Kruis W et al, APT '13; Tursi A et al, APT '13). For example, could this behaviour be linked to the neuronal or motility alteration occurring in diverticulitis (see Simpson J, BJS '03)?

We believe that this discrepancy might be related to the different mechanisms that might underlie to pain genesis in acute and chronic settings. It has been suggested that the pathogenesis of pain in SUDD patients could be related to changes in neuromuscular function secondary to chronic low-grade inflammation differing from pain deriving from acute inflammation.

Discussion section has been modified as suggested.

4. Author stated erroneously reference 9 as study assessing patients suffering from acute uncomplicated diverticulitis. That study doesn't assess acute diverticulitis but SUDD patients. Authors have to cite the study by Parente et al (Parente F. et al, IJCD, 2013) that supports their statement.

We corrected our statement and added a reference to the study by Parente et al. as you suggested.