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Editors-in-Chief
World Journal of Gastroenterology

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March 6th 2019

Dear Professor Ghosh, Dear Prof. Tarnawski,

We would like to express our sincere gratitude for all your efforts in handling and evaluating our manuscript. We were very pleased to read about your offer to submit a revised version of our work to the *World Journal of Gastroenterology*. The authors would like to thank the reviewers and editors sincerely for their time and effort in reviewing our manuscript. We greatly appreciate the excellent comments and suggestions made by the editors and the reviewers and addressed all their concerns in a point-by-point response.

The reviewers and editors' made astute and helpful suggestions that resulted in a substantially improved manuscript. This is especially true in terms of improving the overall clarity of our central message and we thus sincerely hope that you will consider our manuscript for publication.

With very kind regards,

Francesco Vitali (first author)
Timo Rath (senior author)

We appreciate the reviewers' and editors' comments and acknowledge their many contributions to the revised manuscript; thank you! Below are the comment and a point-by-point reply addressing each concern.

Editors' (E) comments to the Author (A) and answer to Editors' comments

1. For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies.

(A) Timo Rath has lived and worked in large parts of his career in the United States and therefore is a native speaker.

2. Please provide point to point answer to all reviewers.

(A) Below are the comment and a point-by-point reply addressing each concern.

3. Similar sentences with other articles (highlighted in the 45333-CrossCheck Report), please rephrase these sentences.

(A) Sentences were change as requested.

4. Please format your manuscript according to the "Formats and Guidelines for Retrospective cohort study".

(A) The manuscript was reformatted according to the Guidelines for retrospective cohort studies.

5. Biostatistics statement

(A) Statistical data were re-assessed and double checked by experienced investigators with profound knowledge in biostatistics (FV, TR, MFN, JS, RA, CN)

6. Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures.

(A) Done

7. Please check and confirm that there are no repeated references!

Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) (Please begin with PMID:)

DOI (http://www.crossref.org/SimpleTextQuery/) (Please begin with DOI: 10.)**

(A) Done

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Reviewers' (R) comments to the author:

Reviewer 1 (R1, Code 00055108):

R1: First: Original findings: Efficacy ST, LT and regardless of it is HS or EC was found, this was the aim of the study. Secondly and thirdly: quality is good, but can be improved - see comments to the manuscript. It is important and add value to the clinical practice. It is hampered by it's method and design.

Authors' reply: We thank the Reviewer for describing our work as important and reading the manuscript so carefully and for the improvement suggested regarding the methods and design. A point-by-point reply addressing each concern is done:

§ Patients and methods:

R1 had several language corrections, all of which were corrected in the revised manuscript.

R1: How many had previously GI-bleeding?

Authors' reply: We applied HP in about 2-3% of the patients with gastrointestinal bleeding in our center. 10% had previous gastrointestinal bleeding with failure of conventional hemostatic approaches such as mechanical or thermal devices or injection therapy or a combination of these.

R1: It states retrospective in your ethical application – please clearify if you retrospectively searched your database or if you planned this study in 2013 i.e. prospectively,

Authors' reply: Our database on hemostatic powders was collected prospectively since September 2013 and the data analysis was performed after completion of follow-up –September 2017- . Ethical approval was obtained before data analysis.

R1: Define clearer the difference between primary/salvage treatment.

Authors' reply: We now clearly define the difference between primary and salvage treatment.
Primary treatment was defined as the first usage of hemostatic powder as monotherapy. Salvage treatment was defined as the usage of hemostatic powder after failure of conventional treatment

R1: Both ST and LT?

Authors' reply: We apologize for the confusion. Rebleeding rate (RBR) describes the rate of patients in which re-bleeding occurred during the 30 days of follow-up.

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§ Clinical characteristics of the patient cohort

R1: This was not clear for me. SD 5.5 months?

Authors' reply: We apologize for the lack of clarity. FU of 3.2 ± 5.5 indeed indicates a mean FU of 3.2 months with a standard deviation (SD) of 5.5 months, as correctly stated by the reviewer.

R1: Define Rockall score: Which one, complete or pre-endoscopy?

Authors' reply: Important point! The complete Rockall score was used in this study. We now clearly describe this in the methods section.

§ Overall Efficacy HP in the management of GI bleeding

R1: Rephrase, delete total, emphazise "primary therapy"

Authors' reply: We re-phrased the sentences as suggested by the reviewer

§ Efficacy of HP in the management of upper GI bleeding

R1: Present the following paragraph only in a Table: "Within the upper GI Tract, bleeding was derived from the following sources: peptic ulcer disease (n=49, gastric ulcer: n=12; duodenal ulcer: n=37), malignant tumor (n=15), esophagogastric varices (n=13), reflux esophagitis (n=12), angiodysplasias or angioectasias (n=8), Mallory Weiss lesions (n=5) and diffuse oozing bleeding and erosions (n=21)."

Authors' reply: We agree that this information can also be conveniently displayed in a table. However, since the manuscript already has numerous tables, we prefer to present these data as a written sentence in the results part. Rescue=salvage

R1: Rephrase the sentence: "Regardless of whether…"

Authors' reply: We rephrased the sentence according to the reviewer's suggestions.

§Discussion

R1 had several language corrections, all of which were corrected in the revised manuscript.

R1: Graphic illustration (Figure 2): what does it add? The 11 studies cited have different designes and so on, and might not be comparable. Fig.2 state that nearly 60% of the patients treated with HP re-bleed at 30 days?? Is that your message?

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Authors' reply: The reviewer is correct that the studies summarized in this table have a different design. Nevertheless and to our own surprise, all these studies consistently show a similar efficacy of HP with almost 100% bleeding control (or close to 0% re-bleeding incidence) and a subsequent increase of the re-bleeding incidence to almost 60% after 30 days of FU, as correctly stated by the reviewer. Therefore, we still feel that this figure enables a quick overview of the results of re-bleeding incidence over time across all the studies published to date.

R1: Do you speculate if there is need for both EC and HS in the endoscopy unit to be prepeared to different situations?

Authors' reply: While our data suggests that both HS and EC have a similar hemostatic efficacy, technical aspects need to be taken into account when applying HS or EC. HS is applied with high pressure and diffusely distributes and therefore can cover large mucosal surfaces within seconds. This might be especially beneficial in situations with diffuse bleeding in large areas such as tumor bleeding. With EC, the pressure of spraying is much lower, allowing a more sectorial area of targeting, making EC more suitable for localized bleeding lesions like a peptic ulcers or a surface after resection.

With discuss these different situations of appliance of HS and EC in the following way in our manuscript:

"Nevertheless, some technical differences between the two HP should be noted: first HS is sprayed at high pressure with a propellant CO_2 cartridge. Such feature might be an advantage in cases of high pressure bleeding or scenarios where a large surface needs to be covered. On the other hand, high- pressure application can potentially cause further tissue injury to the point of perforation especially in friable or inflamed mucosa. Indeed, in two of the patients treated with HS (1.3%), perforation occurred as major adverse events after application of HS in the current study. Occurrence of intestinal perforation after HS application have been reported in other series as well[15,18], therefore some caution of using HS might be necessary. In contrast, with EC the pressure of spraying is much lower, allowing a more sectorial area of targeting, making EC more suitable for localized bleeding lesions like a peptic ulcers or a surface after resection. On the other hand, the area that can be covered with EC might be lower with EC as compared to HS and also high pressure bleeding might be less controlled. However, more systematic studies are clearly needed to investigate on these aspects."

§Figures and Tables:

R1: the pictures misses annotation what is a/b etc. Anatomical loacation in the upper GI-tract?

Authors' reply: We apologize for this oversight. We added a figure legend to s, as suggested by the reviewer and revised the annotations.

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R1: *The present = your study or resent published studies? See also the comment above in the discussion section*

Authors' reply: With the present study, we indeed refer to our own study/data. As suggested by the reviewer, we re-phrased this and also added a figure legend to this figure.

R1: Meaning that 11 patients did get both HP solutions during the same procedure? If so – state that - clearification

Authors' reply: We apologize for the confusion. Indeed, 11 patients were treated with both HS and EC. However, this was not during the same procedure but subsequently at different time points after failure to achieve hemostasis with either HS or EC.

R1: P indcate ns or s between which values??

Authors' reply: The p-value refers to the comparison between HS and EC. A two-sided $p<0.05$ was considered to be statistical significant. Lack of statistical significance is indicated by "ns" (= non significant).

R1: Children are included in your cohort – should be mentioned in patients characteristic.

Authors' reply: We apologize for this oversight. A total of 1 child was included in the study and details were added to the patient characteristics, as suggested by the reviewer.

Reviewer 2 (R2, Code 03713555):

R2: Very nice paper. Your conclusions are supported by results. Well-done.

Authors' reply: We thank the reviewer 2 for these kind words and for describing our manuscript as well written and highly informative

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Reviewer 3 (R3, Code 00055108):

R3: Results can be shown with graphics too.

Authors' reply: Fair point. However, the advantage of presenting the results in Tables is that the reader can directly compare the hemostastic efficacy of the two hemostatic powders in absolute numbers side-by-side. Due to the high numbers of various subgroup analyses in our study (bleeding locale, bleeding source, primary and salvage therapy, re-bleeding rate), we feel that the totality of data can be better and quicker assessed by tables compared to figures or graphs.

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