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World Journal of Gastroenterology

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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6748-Review).

Title: Novel treatment options for perforations of the upper GI tract: Endoscopic Vacuum Therapy and Over-the-Scope Clips.

Authors: Rudolf Mennigen, Norbert Senninger, Mike G. Laukoetter

Name of Journal: World Journal of Gastroenterology

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We thank both reviewers for their comments that have helped us improve the manuscript. Here is a point-to-point-reply to the reviewers´ statements; the according changes were highlighted in the revised manuscript.

Reviewer No. 02533764

1. "This review covered the extended fields, e.g., various organs, various diseases such as postoperative leakage and perforated ulcer, various indication, and two treatments like VAC and OTSC. The theme should be focused on the specific point that authors want to describe. Readers will confuse."

We thank the reviewer for this comment. He points out the main problem of reporting the results of the novel techniques "endoscopic vacuum therapy" and OTSC. First of all, both novel technical developments were used as individual, non-standardized therapies in very different settings. Virtually all publications on these novel techniques include a variety of perforation types, different localizations, and different underlying diseases. Up to now, there is no controlled trial to evaluate the value of these methods.
Concerning the OTSC: Only few studies are focused on a special type of perforation; e.g. Voermans et al., Clin Gastroenterol Hepatol 2012: in this study, 35 out of 36 patients had an acute endoscopic perforation. However, the vast majority of studies lack this standardization. As shown in table 2, most studies

1) are very small, with patient numbers below n=20, and
2) include very heterogeneous types of perforations.

In an effort to organize this heterogenous data pool, we proposed a classification into the three types of perforation "postoperative", "acute endoscopic and interventional

perforations", and "other chronic leaks and fistulas", as we are sure that these types have to be regarded separately due to the completely different settings of these perforations. Most reviews on the success of OTSC closure of perforations provided in the discussions of the papers listed in table 2 only sum up the overall success rate. To the best of our knowledge, we are the first to provide a structured analysis of the otherwise heterogeneous data. Our analysis indicates that acute endoscopic perforations might have a better chance of OTSC closure than other types of perforations.

The same is true for endoscopic vacuum therapy (table 1): the number of available studies is even lower, patient numbers are small, and the largest studies again include postoperative as well as other perforations.

Therefore we feel that the heterogeneity of available studies makes it impossible to focus on only one type of standardized perforation or organ system; in this case, patient numbers would be far too small to draw any significant conclusion.

New and larger studies on the novel techniques are in progress. We are very sure that especially endoscopic vacuum therapy will challenge the previous gold standard "stent therapy" in the upper GI tract. At our institution, we have virtually abandoned stent placement in favor of endoscopic vacuum therapy. During international meetings, the novel techniques endoscopic vacuum therapy and OTSC are intensively discussed. We feel that these techniques will play a very important role in the near future. Therefore we propose to include both techniques in this review, as they can act complimentary in many cases (as in our presented case).

In summary, the approach of our review is to focus on the two novel techniques, not on a special underlying disease. We hope you appreciate our effort to structure the available data on the use of these techniques, although they are very heterogeneous in nature.

We included a discussion of these limitations (which are given by the heterogenity of available studies) in the manuscript on pages 17-18.

2. “In general, perforation needs surgical treatment. Indication of endoscopic treatnment such as VAC and OTSC should be reviewed and shown.”

We appreciate the reviewer´s comment that the indication of endoscopic treatment in upper GI perforations should be reviewed. The second reviewer also commented on the indication of non-surgical treatment (“Surgery is not mandatory to treat these conditions. Please discuss the success rate of conservatory management.”) We included this important aspect in the introduction on pages 4-5. We discuss the circumstances that may allow a conservative or endoscopic management, as opposed to surgical management.

3. “Are placement and removal of EVT reviewed or author’s method? If this manuscript was review article, the methods should be review.”

The reviewer is completely right, we apologize that this was not clarified in our manuscript.
Several centers independently developed the technique of endoscopic vacuum therapy in the upper GI tract. Dr. Loske (Hamburg, Germany) and Dr. Wedemeyer (Hannover, Germany) have to be credited as the first to describe this technique. The principle of application of the vacuum sponge is basically the same in all reports; however, the single endoscopists have slightly different procedures that they found to be most practicable. Based on the published procedures, we adapted the procedure with slight modifications. E.g., the use of a loop at the tip of the sponge has not been described elsewhere.
In the revised manuscript, several modifications of the procedure that can be found in the literature are reviewed, and our own modifications are clearly marked as such.
This important issue is clarified in the methods section and in the EVT section.

Reviewer No. 00183238

1) “This is very interesting article on an innovative approach. It should be presented cautiously because there is a paucity of trials and patients on this procedure.”

We thank the reviewer for this comment. We agree that the available evidence is limited, and the value of these new techniques has to be further evaluated. Therefore we explicitly discuss the limitations of the available literature and data (revised manuscript, pages 17-18). The revised conclusion is worded in a cautious way.

2) “Introduction: Citations for first sentence”

Citations have been added to the list of possible etiologies of upper GI perforations.

3) “Surgery is not mandatory to treat these conditions. Please discuss the success rate of conservatory management.”

The reviewer is completely right that not all perforations mandate surgical management. Reviewer 02533764 had the same remark (see above). In dedicated series, stent therapy of esophageal perforations reaches success rates of about 80-85%. There are no controlled trials comparing surgical management to conservative therapy. All series have a selection bias, as the most critical patients usually mandate surgical therapy. However, if endoscopic or conservative treatment is possible considering the patient´s condition, the outcome of conservative therapy is very favorable and possibly superior to surgical management, as it avoids surgical morbidity.
We discussed the indication of endoscopic therapy of upper GI perforations in the revised manuscript (pages 4-5).

4) “Many typo errors”

We apologize for these typing errors, which have been corrected.

5) “Methods: Not given. Which type of this article is? Case series or literature review or combination? Please explain.”

We thank the reviewer for this important comment. Unfortunately, we did not provide a methods section in the first version of the manuscript; this has been added on pages 5-6. This clearly is a literature review. We discuss the available series on endoscopic vacuum therapy and OTSC closure, and provide a synopsis of success rates in different indications. The description of the procedures is also based on the literature review, and some personal remarks and experiences are added. One clinical case (from our own institution) is presented for illustration purposes, showing the application of both novel techniques in one patient.

6) “Many typo and grammatical errors”

Again, we apologize for the typing errors, which have been corrected. A native speaker has extensively revised the complete manuscript.

7) “No systematic presentation of results”

This review aims to report the development, technical aspects, and results of the two novel techniques, and to discuss their potential value in the management of upper gastrointestinal perforations. To make the presentation of results more systematic, we reorganized the text into “Development, technical aspects” and into “Results” for both endoscopic vacuum therapy and OTSC. In the first mentioned section, the development of the procedure and the technical details of the procedure are reviewed and commented. In the second section, the success rates for different indications are summarized from the

available literature. Tables 1 and 2 report the important synopsis of success rates in the literature.

The value of the novel techniques and their place in treatment algorithms of upper GI perforations is discussed in the section "Therapy algorithms of upper GI perforations including the novel techniques".

We think that this reorganization ensures a more systematic presentation of the review. This structure is explained in the methods section.

We thank the reviewer for this important advice.

8) "Conclusion is missing. This procedure cannot be considered routinely because this is not an RCT."

We have included a conclusion in the revised manuscript. As the reviewer stated, it is worded quite cautiously; as data on the novel techniques are limited, no strong recommendations can be made on their use. Further studies are necessary. However, we are sure that these techniques will play an important role in the near future. The publications of the studies reporting the novel techniques in leading journals such as "Endoscopy" or "Gastrointestinal Endoscopy" (and, if this review should be accepted, World Journal of Gastroenterology) indicates the impact of these novel techniques.

Editor´s comments:

The format has been updated.

Typing errors were corrected.

The references were corrected and formatted.

A native speaker has extensively revised the manuscript and guarantees the language quality of this manuscript.

A longer abstract has been added.

Tables were included in Word format.

Thank you again for all comments on our manuscript which we hope is now suitable for publication in World Journal of Gastroenterology.

Sincerely yours,

Rudolf Mennigen