

Format for ANSWERING REVIEWERS

December 7, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript N6150-review.docx).

Title: Venous thromboembolism in patients with inflammatory bowel disease: Focus on prevention and treatment.

Author: Alfredo Papa, Viviana Gerardi, Manuela Marzo, Carla Felice, Gian Lodovico Rapaccini, Antonio Gasbarrini

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6150

The manuscript has been improved according to the suggestions of reviewers:

Reviewer n.1.

This is a nicely written review on a pertinent topic, and would be a useful addition to the literature. The authors outline several relevant points. Prior to publication, I feel the manuscript can benefit from several modifications as outlined below.

- 1) I think the issue of whether UC, CD, or neither has a higher risk of VTE merits at least brief mention. For instance, references 1, 3, 7, 8 stratify rates by disease type, and this data may be helpful to summarize briefly for the reader (even if rates are similar).
- 2) Although an elaborate discussion of risk factors for VTE in IBD may not be necessary in this review, the manuscript would benefit from a concise, organized mention of the most well-established risk factors. Currently, factors such as younger age and pregnancy are mentioned as risk factors at the end of the epidemiology section, whereas disease activity and prolonged disease course are mentioned at the beginning of the section - this could be better organized. In addition, the statement "...supporting the hypothesis of a greater procoagulant tendency in IBD independent of disease activity" contradicts with statements later in the manuscript pointing out that patients are at greatest risk for VTE during an IBD flare. Is this statement meant to convey that VTE risk is elevated in IBD patients even in the absence of flare, albeit less so than during a flare? If so, this statement should be rephrased to relay this point. Overall, to clarify these issues for readers, I would have a brief but cohesive discussion of risk factors, including an explanation of the role of disease activity in contributing to VTE risk.
- 3) At the end of page 6, in the "Prophylaxis" section, it is stated that "VTE was not associated with major postoperative bleeding." Should this be "VTE prophylaxis was not..."? If so, please correct.
- 4) In the "Prophylaxis" section, there is an emphasis on data examining whether various anticoagulants can be effective for treatment of IBD. While this is interesting, for the scope of this review, it would be more relevant to include any data from these studies reporting adverse events (rates, types, severity, etc.), and any data indicating whether VTE prophylaxis is actually effective in preventing thromboembolism in IBD patients (rather than whether it is effective in treating IBD overall). This later topic is touched upon in the last paragraph ("despite prophylaxis, postoperative thromboembolic events are still frequent" - ref 40), but this deserves further elaboration. For example, is there data indicating VTE prophylaxis is effective in IBD patients, even if no RCT's have been performed? What is the reported rate of VTE despite prophylaxis? Also in this section the authors state that parnaparin sodium may be used "to avoid the systemic effects of anticoagulants...". To what systemic effects does this refer?
- 5) In the "Prophylaxis" section, the first paragraph states "Control of disease activity is crucial to

prevent VTE....” Is there evidence that supports this? If so, I would include the data that supports this statement. If not, I would revise the sentence to reflect that this is mainly supposition.

6) Lastly, given the statement that the inadequate use of VTE prophylaxis in IBD is partially attributed to the lack of awareness of prophylaxis guidelines, I think outlining the current guidelines would be helpful, perhaps in the form of a table. If current guidelines are inadequate or in need of further development, this should be stated.

7) ****The patient information must be removed from the images prior to publication.

Answers to Reviewer 1.

We thank the reviewer for his constructive comments.

1. We added to the text data about incidence rates of VTE according to the different kind of disease (CD or UC).
2. A concise mention and discussion of the well-established risk factors for VTE for IBD patients was added to the text; also the role of disease activity in contributing to the risk of VTE was better explained.
3. We corrected the sentence at the end of page 6 in the Prophylaxis section.
4. We added to the text data regarding the rates of adverse events of anticoagulant therapy (particularly the rates of rectal bleeding) obtained from studies in which anticoagulants were used as a possible treatment of IBD and not for the prevention of VTE. No RCT's aimed to demonstrate the efficacy of VTE prophylaxis in IBD patients have been published. We added to the text the available data regarding the rate of VTE despite postsurgical prophylaxis.
5. We revised the sentence regarding the efficacy of the control of disease activity in preventing VTE in IBD patients. It is only a supposition since we don't have direct evidence for it.
6. We added to the text a table that summarizes the current guidelines regarding the prevention of VTE in IBD patients.
7. We removed the patient information from the images.

Reviewer n.2

I congratulate you on a very nicely written paper that was thorough yet concise. I have a few comments:

1- in your intro you imply that VTE is an extraintestinal manifestation of IBD. I am not convinced that VTE necessarily is an extraintestinal manifestation versus more just a complication of IBD>

2-on page 4 your write Folates - shouldn't it be folate without the s?

3-your CT images has the patient's name on it and this must be removed

4-it would be helpful to cite a reference to support you claim that reason 2 for non-adherence is physicians are concerned about the safety of ppx in patient with active IBD

5-Fondaparinux is a type of lmwh - why do you separate it out? Very nicely done

Answers to Reviewer 2.

We thank the reviewer for his constructive comments.

1. We agree with the reviewer that VTE could be defined as a complication rather than an extra intestinal manifestation of IBD.
2. We modify the text according to the reviewer's suggestion.
3. We removed the patient information from the images.
4. We added some references (n.36,39) to support the sentence that physicians are concerned about the safety of prophylaxis with anticoagulants in patients with active IBD.
5. In the text of the available guidelines regarding the prevention of VTE in IBD patients fondaparinux is mentioned separately from LMWH.

Reviewer n.3

The authors have submitted a review on venous thromboembolism (VTE) risk and management in patients with inflammatory bowel disease (IBD). The topic is highly relevant to current clinical practice. In general, the review provides a concise review with several practical learning points for clinicians. There are several significant areas for improvement within the manuscript:

- 1.) In the introduction, the authors state, "the magnitude of this issue [VTE in IBD] remains underestimated," but the manuscript body contains no information that there is scientific or discrepancy or inaccuracy in the measurement of the magnitude of disease burden. If the underestimation refers to a lack of recognition of risk on the part of clinicians, the text should be changed.
- 2.) In the Epidemiology section, the authors open with estimates of the incidence of VTE in IBD. There are three problems here: 1) incidence units should be events per person-years (not "%"); 2) disease burden at autopsy (ref 5) would include prevalent and incident cases; 3) the post-mortem reference is a 45-year-old abstract, which may not be applicable for current readers. To remedy these problems, please consider dropping data and references to articles 4 and 5 and begin with the properly conducted study to measure incidence, a population-based cohort (ref 7) which provides the appropriate units for incidence (e.g. 31.4/10,000 person-years)
- 3.) In Epidemiology..., the lines beginning with, "Evidence that VTE" and ending with "respect to controls (3)" is a poorly written run-on sentence which concludes with a sentence fragment. Please revise.
- 4.) In pregnant women, please elaborate on "some synergistic prothrombotic mechanism" or consider dropping the speculation.
- 5.) "Risk factor" needs to be plural in several locations throughout the manuscript
- 6.) Elaborate on "hereditary" and "acquired" factors that multiply prothrombotic risk
- 7.) Prophylaxis section cites many circumstantial mechanistic studies but is very short on data substantiating clinical effectiveness of prophylaxis. If there are no studies, especially RCTs to support prophylaxis, suggest either 1) that these be conducted and propose a study design or 2) elaborate on why one cannot be done and 3) identify any relevant observational data (if any).
- 8.) If "the clotting system is involved in IBD pathogenesis" please elaborate on this further.
- 9.) When reviewing clinical trials of heparin or antiplatelet agents, the authors' focus is on clinical efficacy for IBD; instead, if you intend to make an argument about the safety of potential prophylaxis regimens, please provide further detail on adverse bleeding events between treatment and placebo arms .
- 10.) The referenced study showing higher rates of VTE in outpatients compared to hospitalized ones needs further discussion to help the reader understand a counter-intuitive data point which appears to contradict the first sentence of the Conclusion paragraph

Answers to Reviewer 3.

We thank the reviewer for his constructive comments.

1. In the Introduction, we modified the sentence stating that "the magnitude of this issue [VTE in IBD] remains underestimated...." adding to the text that this is due to "a lack of recognition of risk on the part of clinicians", as suggested by the reviewer.
2. We dropped out references 4 and 5 (with their relative data) and we added to the text data regarding incidence rates of VTE in IBD patients, as suggested by the reviewer.
3. We revise this sentence.
4. We dropped out this sentence as suggested by the reviewer.
5. We corrected "risk factors" in "risk factors" where indicated.
6. A concise mention and discussion of the well-established risk factors for VTE (acquired and inherited) for IBD patients was added to the text.
7. No RCT's aimed to demonstrate the efficacy of VTE prophylaxis in IBD patients have been published. We think that RCT's comparing LMWH (or other anticoagulants) to placebo to support

the efficacy of prophylaxis of VTE in IBD patients cannot be conducted for ethical reasons. On the other hand, we can suggest that new studies comparing different kind of pharmacological prophylaxis or comparing mechanical to pharmacological prophylaxis could be conducted. These data were added to the text, as suggested by the reviewer.

8. We added to the text some sentences explaining the role of the clotting system in the pathogenesis of IBD, as suggested by the reviewer.

9. We added to the text data regarding the rates of adverse events of anticoagulant therapy (particularly the rates of bleeding events) obtained from studies in which heparin or antiplatelet agents were used as a possible treatment of IBD and not for the prevention of VTE.

10. We added further discussion to explain the results of the study by Grainge et al. and we also modified the first sentence of the Conclusion paragraph.

Answers to Reviewer 4

The paper reviewed recent data of IBD patients with a high VTE occurrence and possible etiologies. The paper focused on prevention and managements in IBD Patients.

1. Some of the references are not suitable for the publication' requirement, such as World J Surg.,2013.
2. Page 6 in Word format, the number 1. 2. 3. 4. should be replaced by (1) (2) (3) and (4).page 8 is in the same situation1. 2.
3. Page 7 from the day of operation to discharge might be replaced to through.
4. The main parts of the article, that is epidemiology and clinical features... &Prophylaxis against VTE in IBD Pts should be divided into small paragraphs so that readers could read easily.
5. Some references are used so frequently because of its high citation in one article.That need to be revised.

We thank the reviewer for his constructive comments.

1. We modified the references according to the WJG publication's requirement.
2. We modified the numeration at page 6 and 8 according to reviewer's suggestion.
3. We modified the sentence at page 7 according to reviewer's suggestion.
4. We divided the main paragraphs into subparagraphs as suggested by the reviewer.
5. We reduced the number of citations of a single article in the text.

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

Sincerely yours,

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