

Revision Letter

Name of Journal: World Journal of Gastroenterology

Manuscript NO: 47391

Manuscript Type: Meta-Analysis

Dear dr. Jia-Ping Yan,

Please find enclosed our manuscript entitled: 'Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis.' We appreciate the constructive and helpful comments from you and the reviewers, which helped us to improve our manuscript.

Our point-by-point responses to the Reviewers' commentary accompany this letter.

We also edited the manuscript according to your comments. We hope that the revised manuscript now meets the standards of publication in World Journal of Gastroenterology.

Yours faithfully,

On behalf of the authors,

D. Roorda, MD

Corresponding author

Editorial comments

Following the requests of the editor, the following changes have been made to the manuscript. All changes are marked with **yellow**.

- Name of the journal has been added to the manuscript
- Manuscript number has been added to the manuscript
- Manuscript type has been added to the manuscript
- A running title has been added to the manuscript
- Authors with the same affiliation are now listed together before the institution
- The street address of the corresponding author has been added to the affiliation
- Telephone and fax number are added to the contact details of the corresponding author.
- A section describing author contributions has been added to the manuscript
- A conflict-of-interest statement has been added to the manuscript
- An audio core tip has been added to the manuscript (text) and recorded. The audio file will be separately submitted.
- References in the text were correctly formatted, according to the example the editor provided.
- Acknowledgement was added for the support the patient association for Hirschsprungs disease in the Netherlands, for their help in initiating this research project.
- A section containing Article Highlights has been written and added to the manuscript.
- References in the referencelist were correctly formatted, according to the example the editor provided. PMCID were removed. There are no cited articles that have no PMID or DOI.
- Captions were added to figure 2A, 2B and 2C to clarify which figure was A, B and C. Title of Figure 2 was adjusted according to the editors comment.
- Abbreviations in the tables were either fully written out, or an explanation of the abbreviation was provided in the caption.

This is a meta-analysis evaluating the usefulness of Botulinum toxin injection as a treatment for bowel dysfunction, mainly obstructive symptoms and enterocolitis following surgery for Hirschsprung's disease. The results suggested that Botulinum toxin injections are effective for temporary relief of obstructive symptoms especially in the early post-op period. Overall, the manuscript was well written and the study design was proper. It has included all the essential components of a meta-analysis. Although the findings were expected from previous publications and daily clinical practice, this paper has provided the highest level of evidence. Just a few minor comments for the authors to consider

We appreciate the response of reviewer one and want to thank the reviewer for the valuable comments provided and for the time that was spend reviewing our work.

1. Perhaps, the title could be changed to include what specific bowel dysfunction that they are looking for.

Thank you for this suggestion to further clarify the content of our study in the title. The authors considered the title "Botulinum toxin injections for post-operative obstructive symptoms and enterocolitis in Hirschsprungs disease: a Systematic Review and Meta-analysis". As the World Journal of Gastroenterology guidelines prescribe a title of no more than 12 words, we choose to remove the words 'for post-operative obstructive symptoms and enterocolitis' and replace them for 'after surgery'. If formatting and editorial judgement allows for an exception, we are open to change the title back to "Botulinum toxin injections for post-operative obstructive symptoms and enterocolitis in Hirschsprungs disease: a Systematic Review and Meta-analysis".

2. Was there any difference noticed between short-and long-segment diseases?

We agree with the reviewer that this is a very interesting and clinically relevant question. There were only six of the 14 studies included in our systematic review that reported proportions of patients with short segment disease or long segment disease. The current evidence therefore did not allow for meta-analytic testing of differences between short and long-segment disease. Two of the six studies suggested that effectiveness was higher in rectosigmoid disease compared to long-segment disease^{1, 2}. Contrarily, one study found no differences³ and the other three studies did not test for differences between short and long segment disease. This was more extensively added to the Discussion section, page 14.

3. What would be the underlying postulation that enterocolitis could not be improved?

The reviewer makes an important point. There were only three studies reporting on the effects of botulinum toxin injections on the incidence of enterocolitis and the number of patients that were reported with enterocolitis previous to botulinum toxin injections was subsequently small. Our analysis therefore lacked the power to make a more specific point estimate of effectiveness, as shown by the broad confidence interval ranging from effectiveness of 27% to 84%. In response to the reviewers comments and based on our findings, we would therefore suggest that current evidence on the effectiveness of botulinum toxin injections in reducing enterocolitis incidence is not conclusive. We changed this in the Discussion section, page 12-13.

Reviewer 02549885

Authors conducted a meta-analysis on BT injections treatment for obstructive symptoms in HD patients after corrective surgery, and the study indicates that BT injections are effective in treating obstructive symptoms and were associated with mild and temporary adverse effects. This study is interesting

and well conducted, with data analyzing and processing effectively; it is a worthy finding for the treatment of obstructive symptoms after HD surgery. However, there are some problems need to be clearly:

We thank the reviewer for the valuable suggestions, which were used to further clarify the results of our study.

1. As the author described in the introduction, “causes of obstructive symptoms includes: 1) mechanical obstruction, such as anastomotic stricture or adhesions, 2) residual aganglionosis, 3) stool-holding behaviour, 4) general motility disorders of the bowel and 5) anal outlet obstruction”, and as we all known that BT injections cannot be effective to the obstructive symptom caused by residual aganglionosis or bowel motility disorders; it would be more convincing if the author analyzed separately the reason caused obstructive symptoms in this paper.

We acknowledge this as an important factor and agree that this would have been an valuable analysis. In the majority of studies included in our systematic review (8/14) residual aganglionosis or a mechanical obstruction was excluded as a cause of obstruction by barium enema and rectal biopsy before botulinum toxin was administered. The other six studies did not exclude patients with these causes of obstruction from the study, but did not specifically report the cause of obstruction in individual patients prior to botulinum toxin injections. Therefore we could not compare differences in effectiveness of botulinum toxin injections between different reasons of obstructive symptoms. We added this to the limitation of our study in the Discussion section, page 14.

2. This systematic review and meta-analysis searched the Pubmed, Embase and the Cochrane Library, using entry terms of Hirschsprung disease and Botulinum toxin injections; it would be more comprehensive if the author try more entry terms and include the Web of Science database.

We appreciate the suggestion that was made by this reviewer to conduct a more comprehensive search in the available databases. We acknowledge that selection bias is an important concern in meta-analysis. Both the choice for which entry terms are used as well as which databases are searched are important considerations in preventing selection bias. Our entry terms were deliberately limited to only the 'intervention' and 'patientgroup', as we wanted to perform a search as broad as possible, in order to include as much evidence as possible. In response to the reviewers comment we did perform an additional search in Web of Science with our full search strategy (Hirschsprung Disease OR Hirschsprung OR Aganglionic Megacolon OR Congenital Megacolon OR Rectosigmoid Colon Aganglionosis OR Rectosigmoid Aganglionosis OR Congenital Intestinal Aganglionosis OR Colonic Aganglionosis OR aganglionic colon OR aganglionic intestine OR congenital megacolon OR megacolon congenitum) AND (Botulinum Toxins"OR "Clostridium botulinum"OR Botulinum Toxin* OR Clostridium botulinum Toxin* OR Botulin* OR BoTox OR dysport OR xeomin). This search yielded 64 records. Of this 64 records, there were no original studies that met inclusion criteria after title and abstract screening (in addition to already included studies). Our search in Web of Science was added to the methods section, page 6-7 and to Figure 1.*

References of point-by-point response

- 1 Minkes RK, Langer JC. A prospective study of botulinum toxin for internal anal sphincter hypertonicity in children with Hirschsprung's disease. *J Pediatr Surg* 2000; **35**(12): 1733-1736 [PMID: 11101725 DOI: 10.1053/jpsu.2000.19234]
- 2 Patrus B, Nasr A, Langer JC, Gerstle JT. Intrasphincteric botulinum toxin decreases the rate of hospitalization for postoperative obstructive symptoms in children with Hirschsprung disease. *J Pediatr Surg* 2011; **46**(1): 184-187 [PMID: 21238663 DOI: 10.1016/j.jpedsurg.2010.09.089]
- 3 Wester T, Granstrom AL. Botulinum toxin is efficient to treat obstructive symptoms in children with Hirschsprung disease. *Pediatr Surg Int* 2015; **31**(3): 255-259 [PMID: 25616563 DOI: 10.1007/s00383-015-3665-4]

