Peer Review File

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First round of external peer review

Revisions and Responses to Reviewer Comments

Comment 1:

The major limitation of this review is the low quality of the studies included in the review. However, this was inevitable in the current literature, and the authors clearly articulated that the studies had at least a moderate risk of bias.

The authors would have had difficulty assessing the efficacy of the treatment due to the limitation and risk of bias. However, since the main objective of the study was to assess the efficacy, more explanation and comments are essential in the discussion.

Reply 1:

Thank you for the suggestion. We agree that it was difficult to assess the efficacy of botulinum toxin A (BTA) in first bite syndrome (FBS) due to the low quality of the studies available in the literature. There are no standardized scales of symptoms used in the studies and no comparison arms in any of the studies. FBS is known to resolve in many patients spontaneously and identifying the true effect of BTA without having a comparator arm in this situation makes extrapolation of these results very difficult.

Changes in Text 1:

We have added an additional paragraph to address these limitations and the recommendations that can be extrapolated from this study in the discussion. (See Page 14, Lines 358-381)

We have added further background behind the natural resolution of FBS, as well as our theory of the mechanism behind the improvements seen with BTA injection. (See page 13-14, lines 335-349)

We have additionally added a column to Table 7 (Botulinum Toxin A Injection Treatment Dosing and Schedule), commenting on the time from causative surgery to receipt of BTA injection. This leads to further insight and discussion regarding the natural prognosis of the disease and parsing the benefits of the treatment for future studies. (See Pages 33-34/lines 647-660)

Comment 2:

P2 L28-29 (Abstract- objective)
Though the authors' initial intention was to assess the efficacy "compared to conservative measures", this study did not include a comparison with the control or other conservative measures. Therefore, this phrase ("compared to conservative measures") seems inappropriate here.

Reply 2:

Thank you for this suggestion. We agree that this study did not include a comparison with control or other conservative measures, although this was the initial intention of the research study. None of the studies we identified had a control arm.

Changes in Text 2:

We have removed this phrase "compared to conservative measures" or "comparison to conservative measures" from the abstract objectives, introduction, and methods. (See Page 2, line 29-30 and Page 5, line 108 and Page 6, line 121)

Comment 3:

P4 L73

“a fraction of” and “many” are a bit ambiguous and if the authors clarify these with a range of numbers, it would be more informative for the readers.

Reply 3:

Thank you for this suggestion. We agree that these terms are ambiguous and further details can be beneficial to a more sophisticated understanding of the natural resolution of this disease.

Changes in Text 3:

We have removed the phrases “a fraction of” and “many” from this paragraph and replaced it with percentage ranges derived from the literature. (See Page 4, lines 79-82)

Comment 4:

P5 L94-96

It seems that the authors followed PRISMA 2020 checklist, the reference #43 is the older version (2009) of the PRISMA statement.

Reply 4:

Thank you for this suggestion. For the purposes of our study, we utilized the PRISMA 2020 checklist; however, the citation mentions the 2009 version of the PRISMA statement.

Changes in Text 4:

We have replaced the reference with the updated reference for the PRISMA 2020 checklist.

(See Page 5, line 110 and Pag 6, Line 126)

Comment 5:

P6 L117(Materials and Methods - Eligibility criteria)

More description on the exclusion criteria – which was elaborated in the discussion section (P13 L274~) will be helpful to better understand the methods of the study.

Reply 5:

Thank you for this recommendation. We agree that further elaboration of the inclusion and exclusion criteria would help to better understand the methods of the study.

Changes in Text 5:

We have included several additional lines describing the inclusion and exclusion criteria within the “Eligibility Criteria” section. (See Page 6, lines 133-147)

We additionally removed the redundant inclusion/exclusion criteria from within the “Data Source and Search Strategy” Section. (See Page 7, lines 150-153)

Comment 6:

P9 L177-178

It says: “Three studies commented on the occurrence of FBS following external carotid artery (ECA) ligation, from which only three patients had FBS ligation (35,36,38)”. “FBS ligation” looks inappropriate… FBS needs to be changed to ECA or the word ligation needs to be omitted, according to the contents of the included studies.

Reply 6:

Thank you for observing this, this was intended to state “only three patients had ECA ligation.”

Changes in Text 6:

We have removed the word “FBS” and changed to “ECA” in this line. (See Page 9, Lines 216)

Comment 7:

P10 L196

“Six studies assessed patients within one month of treatment” ☾ This part needs citations.

Reply 7:

Thank you for suggesting this revision. We have added these citations.

Changes in Text 7:

We have added the citations for this statement. (See Page 10, line 238)

Comment 8:

P10 L199

“Seven studies assessed patients within four months of treatment” ☾ This part also needs citations.

Reply 8:

Thank you for suggesting this revision. We have added these citations.

Changes in Text 8:

We have added the citations for this statement. (See Page 10, lines 242)

Comment 9:

P10 L206-207 “Average time to the second injection of BTA was 3.75 months (range of six weeks to seven months).”

P10 L208-209 “The second injection was administered on average 3.8 months following the initial injection”

à These two sentences seem like the same content written differently.

Reply 9:

Thank you for identifying this. We have made this change as suggested.

Changes in Text 9:

The initial iteration of this line was removed, and the second line was modified to include “(range of six weeks to seven months).” (See Page 10, Lines 248)

Comment 10:

P12 L258-259

It says, “All treatments involved varying dosages of BTA and ranged from 22.5 U to 75 U and were given at least once and up to five times in some patients”. But according to the Abstract-result and Table 7, the minimum dose of BTA was 10 U.

Reply 10:

Thank you for this observation. This revision suggestion is correct. The dose range is from 10-75U. This has been amended in the text.

Changes in Text 10:

The dose range has been corrected within the body of the paper: “from 10 U to 75 U.” (See Page 13, line 317-318)

Comment 11:

Table 4 Title: Study Quality Assessment for Before-After Studies with no Control Group

--> should be changed to “Study Quality Assessment for Case-series studies”

Reply 11:

Thank you for this observation. This has been amended.

Changes in Text 11:

The title of Table 4 has been changed to “Study Quality Assessment for Case-series Studies.” (See Page 29, lines 626-627)

Comment 12:

The authors do not review the botulinum toxin injection technique in this syndrome. The botulinum toxin is supposed to be injected into the residual parotid tissue. There is really no consensus on how to locate the intraparotid injection site. Some authors use ultrasound (not mentioned by the authors) because one of the possible complications of the use of botulinum toxin (lines 242 to 248) is triggering muscle weakness in the masseter and pterygoid muscles if the injection of the toxin is performed intramuscularly without realizing it.

Reply 12:

Thank you for this suggestion. We further assessed the specifics of injection technique both in further comments in the results and added two additional columns to Table 7 (Botulinum Toxin A Injection Treatment Dosing and Schedule), commenting on the time from causative surgery to receipt of BTA injection and the injection technique used.

Changes in Text 12:

We tried to add as many details on injection technique as possible across all papers into Table 7. (See Pages 33-34/lines 647-660)

We also added line to "Results of Individual Studies" section commenting on ultrasound guidance. (See Page 9, lines 222-223)

Comment 13:

Minor typo. On Line 61 it should say: Netterville et al.

Reply 13:

Thank you for this observation. This line was amended to include this.

Changes in Text 13:

Line was modified to state "Netterville et al (4)." (See Page 4, line 67)

Comment 14:

in the line 61 – should be Neterville et al.

Reply 14:

Thank you for this observation. This line was amended to include this.

Changes in Text 14:

Line was modified to state “Netterville et al (4).” (See Page 4, line 67)

Comment 15:

in the line 176 – it should be used “superficial parotidectomy” not “ lateral parotidectomy”

Reply 15:

Thank you for this recommendation. This wording was changed in the text.

Changes in Text 15:

“Lateral parotidectomy” was changed to “superficial parotidectomy.” (See Page 9, line 214)

Comment 16:

I think that table 2 does not provide more information to the case, as it is described in “Data Source and Search Strategy”

Reply 16:

Thank you for this suggestion. We agree that there is redundancy in the narrative description of the specific database search syntax in the “Data Source and Search Strategy” section.

Changes in Text 16:

Given that it presents redundant information and is well-described within Table 2, we have removed the following phrase: “using a combination of medical subject headings (MeSH) terms

and keywords including: “first”, “bite”, “syndrome”, “botulinum”, “botox”, “botu*” with the Boolean operators “OR” and “AND”. (See Page 7, line 151-152)

We have added additionally included several additional lines describing the inclusion and exclusion criteria within the “Eligibility Criteria” section. (See Page 6, lines 133-147)

Comment 17:

Please add an explanation of the “ND” abbreviation in the Table 7

Reply 17:

Thank you for this observation. We will remove this abbreviation.

Changes in Text 17:

We have removed the abbreviation “ND” from Table 7 and replaced it with “not specified.” Additionally, we have tried to add as many details on injection technique as possible across all papers into Table 7. (See Page 7, line 151-152)

Comment 18:

Line 164: The "," should follow the reference (38).

Reply 18:

Thank you for this observation. We have corrected this stylistic point.

Changes in Text 18:

We have changed the position of the comma to after the parenthesis for this reference. (See Page 8, line 200)

Comment 19:

Line 206-207 reflects the same as Line 208-209 about the average time of the second injection. Please delete one of them.

Reply 19:

Thank you for identifying this. We have made this change.

Changes in Text 19:

The initial iteration of this line was removed, and the second line was modified to include "(range of six weeks to seven months)." (See Page 10, Lines 248)

Comment 20:

Line 220. The acronym PPS has already been specified in the Introduction, Line 60. It is not necessary to repeat the explanation of it.

Reply 20:

Thank you for observing this. We have made the requested change.

Changes in Text 20:

"Parapharyngeal space" is changed to "PPS" within "Results of Individual Studies," as well as within the discussion. (See Page 9, line 213 and Page 11, line 264)

Comment 21:

Line 224. The acronym ITF has already been specified in the Introduction, Line 60. It is not necessary to repeat the explanation of it.

Reply 21:

Thank you for this observation. This substitution has been made.

Changes in Text 21:

“Infratemporal fossa (ITF)” is changed to “ITF” only. (See Page 11, line 269)

Comment 22:

Line 220 and 231. The acronym ECA has already been specified in Line 178. No need to repeat the explanation of it.

Reply 22:

Thank you for this observation. This substitution has been made.

Changes in Text 22:

“External carotid artery” was removed, leaving “ECA” only. (See Page 9, line 216 and Page 11, line 265)

Comment 23:

Line 249: It would be desirable to add "Syndrome" to Eaton-Lambert; also add a "," after Syndrome.

Reply 23:

Thank you for making this suggestion. We have made these changes in the text.

Changes in Text 23:

The line is changed from “myasthenia gravis and Eaton-Lambert and concurrent use” to “myasthenia gravis, Eaton-Lambert Syndrome, and concurrent use.” (See Page 12, line 297)

Comment 24:

Line 237. Botulinum Toxin treatment possibilities are listed. I am surprised that this list does not include Auriculotemporal Syndrome or Frey's Syndrome. I think it should be included.

Reply 24:

Thank you for this suggestion. We have added this into the introduction with new references.

Changes in Text 24:

We have added auriculotemporal syndrome (Frey syndrome) among the uses of BTA with associated references. (See Page 5, lines 97)

Comment 25:

On numerous occasions the word "Botox" is used to refer to botulinum toxin. This should be avoided as it can be confusing with the brand name. Please amend this to "botulinum toxin" or "BTA" (if subtype A).

Reply 25:

Thank you for pointing this out. We have changed this to BTA at all sites, except for where dosing is dependent on the brand name subtype of BTA. Specifically, this is left unchanged in:

Outcomes Assessment:

"Eight of eight (100%) of patients receiving at least 40U of BTA (Botox) had improvement of symptoms at an average of 1.3 months (range one day to four months)" In this line, we did add "BTA" prior to "Botox." (See Page 10, lines 246-248)

Discussion:

"Most patients received BTA (Botox) as the only treatment for FBS; however, there was one patient that underwent two prior tympanic neurectomies (16) and one patient that received gabapentin, BTA (Dysport), and then BTA (Botox) (41)" (See Pages 13, lines 318-319)

Table 7: Botox and Dysport brand names and dosing is mentioned because they are not equivalent. For example, 280U Dysport is much different that 280U of Botox, although they are both BTA. (See Pages 33-34/lines 647-660)

Changes in Text 25:

For changes made from "Botox" to "BTA": (See Page 12, line 299 and Page 12, line 316)

Comment 26:

Line 210: It is postulated that 31.8% of patients have a complete resolution of their symptoms in a mean time of 12.1 months. Could you please reflect in the manuscript what is the theory behind this fact? If the cause of FBS is anomalous parasympathetic activity, how can botulinum toxin

cause a definitive effect. What is the opinion of the authors who refer to this fact in their publications? I think that this fact or at least the theory behind this fact should be specified.

Reply 26:

Thank you for this very important question. Unfortunately, research on cellular models of FBS is not yet available, and it is difficult to fully understand the true mechanism behind this improvement. However, we have provided some of our thoughts on the potential underlying processes that lead to long-term improvements in these patients.

Changes in Text 26:

We have added further background behind the natural resolution of FBS, as well as our theory of the mechanism behind the improvements seen with BTA injection. (See page 13-14, lines 335-349)