Peer Review File

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First External Peer Review

Reviewer A

The manuscript has benefited significantly from the revision. I congratulate the authors and recommend the publication.

Reply: Thank you for your insightful comments, which are undoubtedly much helpful for us to improve the quality of the present paper.

Changes in the text: There was no additional change made in the text.

Reviewer B

This publication presents the case for patient-specific tooth-supported digital guides for balloon compression of the trigeminal nerve. The approach appears novel and unique and, under the conditions given in the study, quite successful. The researchers have conducted a robust pilot study of their guide plate design on a small (n=15) patient population with a singular surgeon. They do an excellent job of providing initially promising results and call for a randomised control trial to evaluate their novel guide plate design on a broader population. Overall, the data presented appear novel, reliable, and repeatable. However, I believe some crucial points of clarification are required before publication.

First and foremost, there is a lack of clarity around some of the statistical results (points 11-14 below). Most important amongst these is the apparent absence of some results, which must be included prior to publication (point 14). Secondly, there may be some rearranging of information, and clarification of references required to establish the novelty of the approach. Evidence of novelty of the device and its theoretical superiority over existing methods is only provided in the discussion and is sparsely referenced (points 8 and 21 below). This information is required in the introduction to justify the device design and the study itself. Thirdly, there is no mention in the discussion of the influence of surgical expertise on the outcome of this study. All procedures were conducted by a single surgeon (line 10), which may be relevant to the procedure's success. To appropriately evaluate whether this guide plate effectively reduces the impact of variations in surgical expertise on patient outcomes (a claim made in the introduction), it would be necessary to provide data for procedures performed by clinicians with varying degrees of expertise. Alternatively, this element of study design

should at least be discussed as a limitation of the research.

Once these main points are addressed, I believe this study would be suitable for publication in Annals of Translational Medicine. All other points made below are suggestions for correction to the authors but do not preclude any recommendation for publication.

1.Claims on line 49-50 require a reference

Reply: Thank you for your careful review and valuable suggestion. We have added the reference needed in the revised manuscript.

Changes in the text: The manuscript has been revised accordingly.

2.On line 59, examples of the specific prescribed drugs would be advantageous

Reply: Thank you for this insightful comment. We have added the sentence "Drugs, such as carbamazepine and oxcarbazepine, have been considered as the first-line agent of symptom controller".

Changes in the text: The manuscript has been revised accordingly.

3.The Hartel anterior approach is mentioned but not described. A brief description (provided on line 71) would be advantageous to readers.

Reply: Thank you for this insightful comment. We have added a brief description of the Hartel anterior approach in the revised manuscript.

Changes in the text: The manuscript has been revised accordingly.

4.On line 78, examples of the specific sequelae of postoperative complications would be helpful

Reply: Thank you for this insightful comment. We have added the sentence "such as more severe trauma, more severe numbness, bleeding and so on".

Changes in the text: The manuscript has been revised accordingly.

5.A synopsis of the advantages of this particular guide plate over existing guide plates, and current methods is necessary to establish the novelty of this research. This could be addressed on line 86.

a.This information is provided in the discussion (lines 234-250). To establish novelty of research and justification for testing, this information should be relocated to the introduction.

Reply: Thank you for this insightful comment. We have added a summary of advantages of this tooth-supported guide plate over the existing guide plate in the introduction section.

Changes in the text: The manuscript has been revised accordingly.

6.It would be valuable to place a copy of the patient consent form in the supplementary

material (and reference this on line 96)

Reply: Thank you for this insightful comment. We have added the informed consent form (original version and English translation version) in the supplementary materials.

Changes in the text: We have added the content form (original version and English translation version) in the supplementary materials accordingly.

7.Line 106-107 makes mention of a complete summary of inclusion criteria of patients but does not provide a reference of where this summary can be found. If researchers are referring to Table 1, then this should be stated in the text.

Reply: Thank you for this insightful suggestion. We have supplemented the references of the indications of balloon decompression for trigeminal neuralgia accordingly.

Changes in the text: The manuscript has been revised accordingly.

8.What additional benefit is derived from matching CT models to gypsum impression models? This is not explicitly discussed in the methods or introduction.

a.This information is provided in the discussion (lines 234-250). Once again, it would be beneficial if this was relocated to the introduction.

Reply: Thank you for this insightful comment. The information has been relocated.

Changes in the text: The manuscript has been revised accordingly.

9.On lines 118-119, the researchers state that "CT data were converted into 3D reconstructions with Mimics 17.0 software". Was this reconstruction conducted using manual or automatic segmentation methods? If the reconstruction methods were manual or a combination of automatic and manual, how do researchers propose to standardise these methods for clinic use? If the reconstruction is automatic, please specify which tools were used.

Reply: Thank you for this insightful comment. This reconstruction was conducted using automatic segmentation methods, which was provided in Mimics 17.0 software.

Changes in the text: The manuscript has been revised accordingly.

10.On line 134, researchers state that a single surgeon operated on all patients. This is an excellent approach to ensure that all patients receive the same treatment and that patient results are not affected by variations in surgical technique and expertise. However, it does raise the question of how much experience this particular surgeon has with fitting these guide plates and whether the same results could be replicated with a different surgeon. In this publication, it would be important to summarise the expertise/experience of this surgeon and mention the impact of this expertise in the discussion. Also, one of the principal stated advantages of this novel guide plate was the ability for novice clinicians to perform these surgeries. Thus, a future study would benefit from a randomised control trial of this guide plate against existing methods, with surgical experience included as a factor. An alternative approach would be to repeat this study with surgeons of varying experience.

Reply: Thank you for this insightful comment. In order to reduce the influence of the operator on the research results, the 15 patients included in this study were implemented by the corresponding author of this study, Dr. Minjie Chen; and there were about 50 sets of foramen ovale puncture for trigeminal neuralgia in our research group every year, most of which were performed by Dr. Minjie Chen. The tooth-support digital guide plate used in this study is fixed on the intraoral dentition with repeatable retention stability. When the dental support digital guide plate was used, the novice clinicians in our research group can greatly reduce the difficulty of puncture through oval foramen (empirical results)

Changes in the text: The details were supplemented in the revised manuscript.

11.Statistical analysis would benefit from some correction for multiple hypothesis testing, depending on the number of tests conducted. As not all statistical results are presented, it is difficult to ascertain how many statistical tests were performed. However, at least 4 tests were conducted on the VAS scores alone.

Reply: Thank you for your careful review and valuable suggestion. The Bonferroni correction was conducted for multiple comparisons in the revised manuscript.

Changes in the text: The Bonferroni correction was supplemented in the revised manuscript.

12.Statistical analysis would also benefit from proof of evaluating parametric assumptions of data (testing for normal spread). This is particularly relevant with regard to the paired t-tests, as the small sample size might preclude parametric testing.

Reply: Thank you for your careful review and valuable suggestion. After Kolmogorov-Smirnov test, the VAS of each timepoint obeyed normal distribution (all P <0.05).

Changes in the text: The details were supplemented in the revised manuscript.

13.Is there a statistical reason that researchers have referenced two separate significance thresholds (line 185 – P<0.001 and line 162 – P<0.05). If P<0.05 is the significance threshold for all tests, as stated on line 162, then this is the threshold that should be stated throughout the publication (e.g., Table 4). If different thresholds are to be used for different tests, some justification ought to be provided.

Reply: We are sorry for your misunderstanding. We only used one significance threshold for all tests (P < 0.05). The P <0.001 in Table 4 was not another significance threshold, it was the expression that the P value obtained by the test was too small to display the specific value.

Changes in the text: There was no additional change made in the text.

14.To the best of my understanding, it appears that results of statistical tests mentioned on lines 161-163 are not presented. The only statistical results table presented contains paired t-test results for VAS scores. All statistical results (even non-significant) should be presented.

Reply: Thank you for your careful review. Table 3 displayed the longitudinal changes

of the Trigger point, Attack frequency per day, Attack duration and BNI pain intensity score across the 6 timepoints. The statistical results were supplemented in the revised manuscript.

Changes in the text: The details were supplemented in the revised manuscript.

15.On line 182, there is mention of a single patient with intolerable pain at T3 and the subsequent postoperative pain management (Carbamazepine). Were there subsequent follow-ups with this patient? These follow-ups could perhaps address some of the following questions that would be relevant to device design:

a.Was there any investigation as to whether any aspect of the balloon procedure was the instigator of subsequent T3 pain?

b.Were pain scores before and after surgery comparable?

c.Were there specific co-morbidities that may have contributed to the failure of the treatment? That could be investigated as contraindications in future.

Clarification on these questions is not necessary but may be beneficial to evaluating guide plate performance.

Reply: Thank you for this insightful comment. We have followed up with this patient closely. At present, the patient was treated with low-dose carbamazepine, and the pain can be completely controlled. In the future, we will conduct further research according to your guidance and our established research plan

Changes in the text: This question was addressed in the above reply, with no additional changes made in the text.

16.Throughout the study, there is mention of confirmatory CT conducted in all patients. Given that one of the key advantages of this technique would be the reduction of unnecessary radiation exposure, it would be beneficial if researchers discussed/evaluated whether this CT was necessary for successful guide insertion. Researchers describe adjustments that were necessary but do not confirm that these adjustments were made on the basis of CT scans. If the successful use of this guide plate still requires intraoperative radiographic guidance, it would be important to mitigate claims made in the introduction about the advantages of this guide plate over existing methods. Perhaps researchers could make some numerical comparison regarding the amount of radiation exposure required in traditional procedures vs procedures that are accompanied by their guide plates.

Reply: Thank you for this insightful comment. Throughout the study, the confirmatory CT conducted in all patients was used to confirm the accuracy of the digital plate, as a tool for validation. All patients have signed informed consent. In traditional surgery, this verification process was essential and even needs to be carried out several times. But with the help of the plate, this process only needed once or even omitted.

Changes in the text: This question was addressed in the above reply, with no additional changes made in the text.

17.Reference is required for claims made on lines 213-214.

Reply: We added a reference to support this viewpoint in the revised manuscript (PMID: 25807330, 26236998, 32619112).

Changes in the text: The manuscript has been revised accordingly.

18.Reference is required for claims made on lines 215-216

Reply: We added a reference to support this viewpoint in the revised manuscript (PMID: 26236998, 2294184).

Changes in the text: The manuscript has been revised accordingly.

19.On lines 217-218, there is mention of anatomical variations that are contraindications for the Hartel anterior approach. Examples of these anatomical variations would be very valuable. If researchers are referring to pterygoid and pterygospinous ligaments, this should be specified.

Reply: Thank you for this insightful comment. The information has been supplemented in the revised manuscript.

Changes in the text: The manuscript has been revised accordingly.

20.Reference is required for claims made on lines 219-220. If no reference/published data is available, evidence of data from a specific surgeon or a testimonial from a particular surgeon would suffice.

Reply: We added a reference to support this viewpoint in the revised manuscript (PMID: 26236998).

Changes in the text: The manuscript has been revised accordingly.

21.Claims made on line 223 that currently used guide plates and navigation techniques have "poor stability and great trauma" require clarification and references. It is important that these claims be clarified to establish the novelty of this particular guide plate over existing methods.

a.These points are clarified in lines 234-250 of the discussion. If this section was relocated to the introduction, all previous comments regarding this issue would be addressed. However, this section (234-250) would still need adequate references, which it currently lacks.

Reply: We added more references to support this viewpoint in the revised manuscript (PMID: 26236998). In the other hand, we also used the methods, such as electromagnetic navigation and mask-like guide plates for RFT. We found that due to the yielding of soft tissue and the uncertainty of intraoperative mandibular position, these methods lack sufficient stability.

Changes in the text: The manuscript has been revised accordingly.

22.On line 279, researchers state that "the guide was produced personally". Based on the sentence that follows, I presume the researchers are referring to the fact that guides

are patient-specific rather than ‘produced by the patient’. Thus, for clarity, the sentence should read "the guides are patient-specific".

Reply: Thank you for your careful review. We have revised the sentence to avoid ambiguity.

Changes in the text: The manuscript has been revised accordingly.

23.A general comment on the device design: Have authors investigated how the length of the insertion guide affected results? If so, a description of that investigation in the article would be an excellent addition to the paper. If not, mention of this in the discussion would be valuable.

Reply: Thank you for this insightful comment. In this study, due to the needs of preoperative design and surgical simulation, the cannula we selected has been produced and applied in clinic (Shenzhen Shineyard Medical Device Co., Ltd., CTZ-15 L), and we scanned the cannula digitally. Therefore, the preoperative design of the guide plate will match this cannula, that is, the distance from the starting section of the guide rail to the foramen ovale is fixed. Due to the differences of anatomical structures of different patients, the intraoperative operation reflected different puncture angles, puncture mucosal positions and guide plate guide rail lengths.

Changes in the text: This question was addressed in the above reply, with no additional changes made in the text.

24.A general comment on study design and manuscript: It is clear that this study is presenting an alternative and novel approach to trigeminal nerve balloon compression, rather than demonstrating that this new approach provides a statistically significant improvement in outcomes over traditional methods. Given that this study is not a randomised control trial or even a comparison of multiple methods, it would be valuable to clarify the scope of the study (aka pilot study) explicitly in the introduction.

Reply: Thank you for this insightful comment. The study design is more clearly clarified in the introduction.

Changes in the text: The manuscript has been revised accordingly.

Reviewer C

I've read the Draft carefully.
Kudos to the author's clinical idea.

There are a few questions, and I think they need to be supplemented for publication.

1. I think that the fit of the guide in the oral cavity is closely related to the number of remaining maxillary teeth. I would like data about the number of teeth to be added to the patient's demographic data. Also, this idea can be applied to dentition patients, but I would like to add consideration to how to increase the suitability of the guide in edentulous patients.

Reply: Thank you for this insightful comment. The information of maxillary residual teeth number of included patients was supplemented in the revised. The plate was placed on the teeth of the entire maxilla. Therefore, a desolated tooth status or dental treatment, especially edentulous jaws, might make the application of the guide more difficult. To address this problem, we needed to obtain the patients' data 3-5 days before the operation to avoid sudden changes in the state of the teeth. A problem with a single tooth will not affect the stability of the whole guide plate, as appropriate grinding can adjust the corresponding position of the guide plate. For patients with edentulous jaws, we have implemented the "complete denture"-like plate. Nevertheless, further improvements are needed

Changes in the text: The details were supplemented in the revised manuscript.

2. In the text, it was said that the CT confirmed whether the needle tip reached the foramen ovale correctly, but plain film is displayed in the figure. Of course, CT is accurate, but in the presence of an endotracheal tube, CT is difficult in common sense. I would like to clearly describe the radiological method that will prove the correct insertion of the needle.

Reply: Thank you for this insightful comment. In our study, all operations were performed under intravenous anesthesia without endotracheal intubation and ECG monitoring. Therefore, it will not have adverse effects on CT examination.

Changes in the text: The details were supplemented in the revised manuscript.

Second External Peer Review

Reviewer A

The authors have done an excellent job at responding to all of the concerns raised. I have just a few responses to their replies to each of my original comments. I also have some additional comments regarding the revised manuscript. Please find both below.

Replies to reviewer comments

8. What additional benefit is derived from matching CT models to gypsum impression models? This is not explicitly discussed in the methods or introduction. This information is provided in the discussion (lines 234-250). Once again, it would be beneficial if this were relocated to the introduction.

Reply: Thank you for this insightful comment. The information has been relocated.

Changes in the text: The manuscript has been revised accordingly.

Response to reply 8: This information still appears to be in the discussion (lines 252-265). It ought to be relocated to the introduction or to the methods to justify the use of this technique.

Reply: We are sorry for this mistake in the last round. The information has been relocated in the revised manuscript now.

Changes in the text: The manuscript has been revised accordingly.

9. On lines 118-119, the researcher's state "CT data were converted into 3D reconstructions with Mimics 17.0 software". Was this reconstruction conducted using manual or automatic segmentation methods? If the reconstruction methods were manual or a combination of automatic and manual, how do researchers propose to standardise these methods for clinic use? If the reconstruction is automatic, please specify which tools were used.

Reply: Thank you for this insightful comment. This reconstruction was conducted using automatic segmentation methods, which was provided in Mimics 17.0 software.

Changes in the text: The manuscript has been revised accordingly.

Response to reply 9: There is still no mention of 'automatic segmentation' anywhere in the revised manuscript. This should be specified in the manuscript to highlight the repeatability of guide creation. Also, this is important methodological information.

Reply: Thank you for this insightful comment. First, the CT data was imported to Mimics 17.0 software. Next, according to the different thresholds of image data, the bone tissue was separated from surrounding soft tissue. Thus, we obtained the imaging data of all cranial and maxillofacial bone which can be reconstructed in the 3D model by Mimics 17.0 software. With the help of this software, we can process the determined part of the data to obtain the 3D model of the specified bone.

Changes in the text: We have supplemented the details of 3D reconstructions with

Mimics 17.0 software in the revised manuscript.

10. On line 134, researchers state that a single surgeon operated on all patients. This is an excellent approach to ensure that all patients receive the same treatment and that patient results are not affected by variations in surgical technique and expertise. However, it does raise the question of how much experience this particular surgeon has with fitting these guide plates and whether the same results could be replicated with a different surgeon. In this publication, it would be important to summarise the expertise/experience of this surgeon and mention the impact of this expertise in the discussion. Also, one of the principal stated advantages of this novel guide plate was the ability for novice clinicians to perform these surgeries. Thus, a future study would benefit from a randomised control trial of this guide plate against existing methods, with surgical experience included as a factor. An alternative approach would be to repeat this study with surgeons of varying experience.

Reply: Thank you for this insightful comment. In order to reduce the influence of the operator on the research results, the 15 patients included in this study were implemented by the corresponding author of this study, Dr. Minjie Chen; and there were about 50 sets of foramen ovale puncture for trigeminal neuralgia in our research group every year, most of which were performed by Dr. Minjie Chen. The tooth-support digital guide plate used in this study is fixed on the intraoral dentition with repeatable retention stability. When the dental support digital guide plate was used, the novice clinicians in our research group can greatly reduce the difficulty of puncture through oval foramen (empirical results)

Changes in the text: The details were supplemented in the revised manuscript.

Response to reply 10: I can now see that there has been inclusion of the surgeons details (Dr. Minjie Chen). However, there is still no reference in the discussion about the decision to only have one surgeon perform all procedures, and the impact this experimental design has on the validity of conclusions such as 'The operation is more approachable for young, 42 novice surgeons' (line 41-42). This study has not evaluated how easy the procedure is to perform for novice surgeons, as there is no mention of the experience level of Professor Chen. These details will need to be included to support the validity of such claims.

Reply: Thank you for this insightful comment. In order to reduce the influence of the operator on the research results, the 15 patients included in this study were implemented by the corresponding author of this study, Dr. Minjie Chen, who performs at least 50 such operations every year. In the other hand, an experienced surgeon can ensure the smooth completion of the operation and avoid the failure of the operation due to the ineffective guide plates. The tooth-support digital guide plate used in this study is fixed on the intraoral dentition with repeatable retention stability. First, the direction and depth of the guide plates are unique; Secondly, the stability of guide plates retention. These two points determined that the operator can only operate according to the preoperative design without the possibility of adjustment based on her own experience. In all operations, all guides were effective. Therefore, we believe that this guide can provide more convenience for novice surgeons.

Changes in the text: The details were supplemented in the revised manuscript.

13. Is there a statistical reason that researchers have referenced two separate significance thresholds (line 185 – $P<0.001$ and line 162 – $P<0.05$). If $P<0.05$ is the significance threshold for all tests, as stated on line 162, then this is the threshold that should be stated throughout the publication (e.g., Table 4). If different thresholds are to be used for different tests, some justification ought to be provided.

Reply: We are sorry for your misunderstanding. We only used one significance threshold for all tests ($P < 0.05$). The $P <0.001$ in Table 4 was not another significance threshold, it was the expression that the P value obtained by the test was too small to display the specific value.

Changes in the text: There was no additional change made in the text

Response to reply 13: Excellent, thank you for the clarification and my apologies for my misunderstanding. In future, one way to avoid confusion is to use a capital P for thresholds and a lower case p when stating the actual p value in tables.

Reply: Thank you for your insightful recommendation, we have revised the manuscript and tables accordingly.

Changes in the text: The manuscript and tables have been revised accordingly.

14. To the best of my understanding, it appears that results of statistical tests mentioned on lines 161-163 are not presented. The only statistical results table presented contains paired t-test results for VAS scores. All statistical results (even non-significant) should be presented.

Reply: Thank you for your careful review. Table 3 displays the longitudinal changes of the Trigger point, Attack frequency per day, Attack duration and BNI pain intensity score across the 6 time points. The statistical results were supplemented in the revised manuscript.

Changes in the text: The details were supplemented in the revised manuscript.

Response to reviewer comment 14: Excellent, thank you. If possible, these statistical results should be provided in a supplementary table.

Reply: Thank you for your insightful comments, .

Changes in the text: There was no additional change made in the text.