

Peer Review File

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Reviewer A:

Comment 1: Please provide proper patient selection criteria for mandible advancement. MA group showed significant class II tendency compared to WoMA. The baseline evaluation is crucial for evaluating changes of the airway dimensions.

Reply 1: The selection criteria for mandibular advancement in MA group were as follows:

1. Patients had a skeletal Class II;
2. SNB less than 73°;
3. Patients required to improve the mandibular retrusion deformity;

We have added these criteria in the manuscript, and highlighted in red (Line 116-119).

Changes in the text: *The proper patient selection criteria for mandible advancement in MA group were as follows: 1) patients had a skeletal Class II; 2) SNB less than 73°; 3) Patients required to improve the mandibular retrusion deformity.*

Comment 2: I recommended adopting repeated measure ANOVA for statistical analysis. Multi-use of t-test may result in accumulation of alpha-error.

Reply 2: Thank you so much for your suggestion. In this study, each patient was measured at two time points (T1 and T2), and for that, the paired t-test was used to compare the differences at T1 and T2 within the same group. An independent sample t

test was used for the comparison of the measurements between the groups. We apologize for the confusion in the submitted manuscript, that we did not express it clearly in the former manuscript, and we have made the revision in the statistical analysis part accordingly, and highlighted in red. (Line 181-183)

Changes in the text: *The changes of the upper airway and hard tissue were compared at T1 and T2 within the same group by using paired t test. An independent sample t test was used for the comparison of the measurements between the groups.*

Comment 3: Sex distribution and bilateral/unilateral side prosthesis may influence the results of the study. Those factors should be considered as confounding factors in statistical analysis.

Reply 3: Thank you so much for such an interesting and critical comment. We performed the statistical analysis, and only found that the changes of SD2 (P<0.05) and SD3 (P<0.01) were significantly different between genders in the MA group. And there was no difference of changes between bilateral/unilateral side prosthesis in both groups. We thought that the limited number of cases and hence smaller sample size may be one of the reasons, which we mentioned in the revised manuscript as one of the limitations of this study. We believe that more interesting results would be found with accumulating cases in larger sample size studies. We mentioned that clearly in the discussion section in the limitations of the study, and highlighted in red. (Line 340-342)

Changes in the text: *Second, the number of included cases was limited. Hence, a greater number of patients would be necessary to investigate further differences*

between genders or bilateral/unilateral side prosthesis.

Reviewer B:

Comment 1: No specific details regarding patient consent. Your manuscript does not contain a complete IRB statement regarding ethics board approval. Original articles need to contain a statement about the Helsinki Declaration of 1975, as in the example given here: “This study was approved by the human subjects ethics board of XXXXX and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Reply 1: Thank you for your comment. An informed written consent was signed by all participants of the study, and this was declared at the end of Ethical Statement (Line 394). And we revised the IRB statement according to the proposed example, and highlighted in red in the revised manuscript. (Line 103-105).

Changes in the text: *This study was approved by the Independent Ethics Committee of Shanghai Jiao Tong University School of Medicine affiliated 9th People’s Hospital and was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2013).* (Line 103-105)

Comment 2: CT section needs further description regarding the complete CT protocol.

Reply 2: Thank you for your suggestion. The detailed description of CT protocol applied in the current study was added in the revised manuscript in the Measurements section of Materials and Methods and highlighted in red as follows:

Changes in the text: *The TMJA patients' spiral maxillofacial CT scans were taken before operation (T1) and at least 3 months (T2) after surgery for all patients. The CT protocol for evaluation included axial images (matrix size 512 x 512, 120 kVp) of 1 mm thickness from the top of the frontal sinuses to the bottom of the mandible. Coronal and sagittal reformats were reconstructed at 0.625 mm intervals.* (Line 146-150)

Comment 3: Please provide this information in Measurements:

.....metrical assessment was performed by one investigator.... Years of practice? Where were the analyses performed (computer details)?

There must be much more detail about how the images were measured and calculated.

Please, include figures that show the measurements for those of us who have not done this by ourselves.

Reply 3: The further information of investigator and computer have been added in Measurements. The methods about how the images were measured were detailed in Table 1, Table 2 and Table 3.

Changes in the text: ...*one investigator (Li H, 13 years of practice)*... (Line 156)

The details of the computer system performing the analyses were as follows: operating system, windows 7 64-bit; central processing unit, Intel(R) Core(TM) i5-3350P; random access memory 4 GB. (Line 157-159)

Regarding the second point of adding more details about how the images were

measured and calculated. We included a new figure that show the measurements referred as **Fig. 1.**

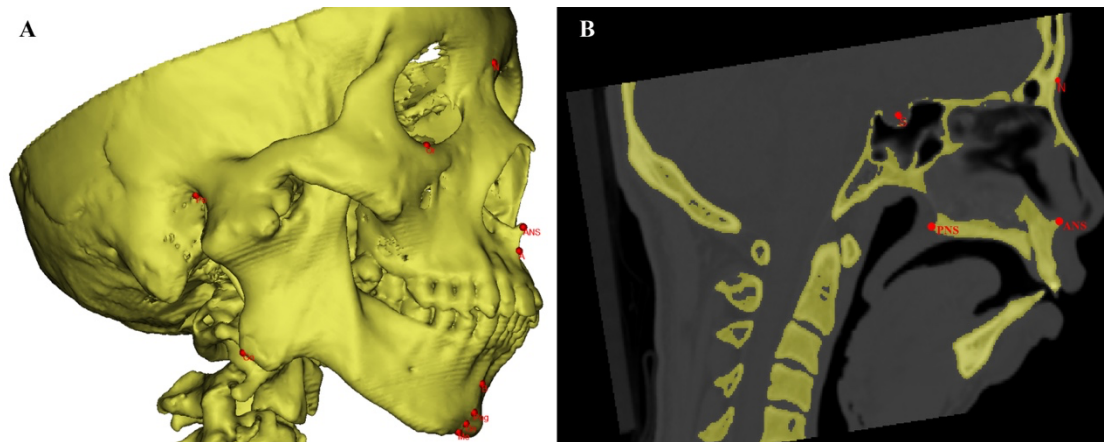


Fig.1 Landmarks of maxilla and mandible: S, Sella; N, Nasion; Or, Orbitale; Po, Porion; A, Point A; B, Point B; ANS, Anterior nasal spine; PNS, Posterior nasal spine; Go, Gonion; Me, Menton; Pog, Pogonion; Gn, Gnathion

Comment 4: The Discussion is slightly disorganized and it is difficult to determine what points are based on the author's study, their conjecture, or previously published literature. The Limitations section should be expanded to include concerns raised in Weaknesses.

Reply 4: Thank you so much for your comment. We revised the discussion section according to the reviewer suggestions and changed accordingly, emphasizing the different points related to our study, to our conjecture and those points related to previous reports. We changed in the manuscript and highlighted in red. Please check the discussion section in the revised form.

Regarding the second point of the 4th comment concerning the limitations of the study, we revised that part and changed accordingly and highlighted in red in the revised manuscript as follows: (Line 337-348)

Changes in the text:

Still this study has some limitations. First, the follow up period after total TMJ prostheses replacement was only 7.1 months on average. Therefore, longer-term follow up periods would be needed to evaluate the changes of the airway dimensions and stability of the hard tissue. Second, the number of included cases was limited. Hence, a greater number of patients would be necessary to investigate further differences between genders or bilateral/unilateral side prosthesis. Third, the data of patients' height and weight were not collected in the current study. The correlations between changes of the airway dimensions and height, weight or body mass index (BMI) could not be examined in this study. Fourth, according to the records, there were some patients with complains of sleeping apnea or snoring. But they did not undergo polysomnography before or after surgery. In further future prospective studies, better designed research methods and more detailed data will find more interesting results.

Comment 5: An added point to Discussion section would be to discuss this recent paper about the upper airway volume: <https://pubmed.ncbi.nlm.nih.gov/33719936/>

Reply 5: This article investigated the relationship between the movements of the TMJ and the variation in the upper airway volume in a clever and scientific way. It has been

added in the text.

Changes in the text: *In Costa et al.'s study (14), it was revealed that the mandibular rotation (open- and closed-mouth positions) alone could change the volume of upper airway.* (Line 304-306)

Reference (14) (Line 435-437)

Reviewer C:

Comment 1: The authors do not mention the TMJ prosthesis that was used for all patients.

Reply 1: Thanks for the reviewer's reminding. It was not clearly mentioned in the text.

We added it in the text (Technique of operation). (Line 122-123)

Changes in the text: *All patients underwent bilateral/unilateral condylar reconstruction with Biomet standard prosthesis (Biomet, USA).*

Comment 2: Please improve the surgical description (technique of operation).

Reply 2: The revisions were made in the text and highlighted in red. (Line 123-143)

Changes in the text:

*Modified preauricular incision was used to expose the bony fusion and upper part of the ramus, **combined with a** retromandibular incision to expose the lower part of the ramus. Digital guides were applied to help removing bony fusion, trim extensive bone spurs in the condylar neck, bone grafting and also aid **a precise** placement of the prosthesis.*

Combined procedures:

Procedure A, coronoidotomy: the ipsilateral coronoid process was removed, simultaneously with release of the temporalis muscle.

Procedure B, LeFort I osteotomy: the incision was made from first molar to first molar with 5 mm of sliding gingival cuff kept on the maxilla. Then, both the lateral and medial buttresses of the maxilla were exposed. Digital guides and surgical splint were applied to help perform the osteotomy and movements of the maxilla and achieve the preoperative plan.

Procedure C, sagittal split ramus osteotomy (SSRO): in patients with unilateral TMJ ankylosis, SSRO was performed on the contralateral side when mandibular asymmetry was encountered or mandible advancement was needed. Digital guides and surgical splint were applied to help perform the osteotomy and movements of the mandible.

Procedure D, genioplasty: the incision was made maintaining 5 mm of sliding gingival cuff. Medial buttress of the chin was exposed, then the digital guides were applied to help perform the osteotomy and movements of the chin and achieve the preoperative plan.

Comment 3: Standardization of acronyms throughout the manuscript: i.e., after the first citation of cross-section area (CSA) in the manuscript, there is no need to write again cross-section area. Please double check all acronyms in the manuscript for consistency.

Reply 3: The acronyms have been checked in the text.

Changes in the text: *Line 52, 65, 66, 99, 353, 354 mandibular advancement MA*

Line 280, 299, 308 cross-sectional area CSA

Comment 4: The authors could include a column in Table 4 with the post-op CT scan period for each patient.

Reply 4: The column has been added in Table 4 as “Follow up (month)”.

Changes in the text: please check the highlighted in red in Table 4 as follows:

Table 4 Information of the TMJ ankylosis patients treated by total TMJ prosthesis

No.	Gender	Age at surgery (year)	Age of onset (year)	Course of disease (year)	Group	Sides*	Combined Procedures**	Follow up (month)
1	Male	41	13	28	MA	Bi	A+B	7
2	Male	59	56	3	WoMA	Bi	/	27
3	Female	32	8	24	MA	Bi	A+B+D	5
4	Male	43	9	34	MA	Bi	A+B+D	9
5	Female	52	32	20	WoMA	Bi	A	3
6	Female	39	10	29	WoMA	Uni	D	8
7	Female	62	22	40	WoMA	Uni	/	3
8	Female	25	10	15	WoMA	Uni	A+B+C+D	5
9	Female	48	7	41	MA	Uni	A+C+D	3
10	Female	20	10	10	MA	Uni	B+C	13
11	Female	53	4	49	MA	Uni	A+B+C+D	8
12	Female	23	4	20	MA	Uni	B+C+D	3

13	Female	27	13	14	WoMA	Uni	B+C+D	3
14	Male	27	22	5	WoMA	Uni	A	3

*: Bi=bilateral, Uni=unilateral

** : A, coronoidotomy; B, LeFort I osteotomy; C, SSRO on the opposite side; D, genioplasty

Reviewer D:

Comment 1: As the group selection has been made retrospectively on the basis of the mandibular advancement obtained is difficult to assess any correlation between the surgical approach and the enlargement of the upper airways.

Reply 1: Yes, it is difficult to assess any correlation between the enlargement of the upper airways and the surgical approaches, except for mandibular advancement. And it was shown that there was no difference of upper airway or hard tissue changes in patients that had bilateral total joint replacement vs. unilateral total joint replacement in this study. The limit number of cases may be one of the reasons. According to the results and articles we reviewed, MA would be the most important surgical procedure to increase the dimension of upper airway according to the results in this study. Other combined procedures had their own different goals. Coronoidotomy was aimed to release extra-articular tension. LeFort I osteotomy and SSRO were planned when correction of facial asymmetry or MA was needed. Genioplasty would be performed for further correction of mandibular retrusion.

Comment 2: No ethical committee number has reported.

Reply 2: The ethical committee number was SH9H-2014-46. It was showed in the Trial registration (Line 71) and Ethical Statement (Line 393).

Comment 3: I would eliminate Table 7 as Y-axis is mostly affected by verticality I do not see the need to highlight these correlations.

Reply 3: Thank you so much for the suggestion. We would like to keep the data of Y-axis angle. Because the Y-axis angle reflects the positional relationship between the mandible and the anterior skull base plane. If the Y-axis angle increased, the lower jaw would become backwards, and the face would mainly change vertically. If the Y-axis angle decreased, the lower jaw would be protruding, and the direction of the change of face is forward. Hence, we think that a linear data and an angle data could reflect the mandibular advancement more comprehensively, and the changes of upper airway more explicitly.

Comment 4: I would suggest authors specify when do these patients suffer from TMJ-ankylosis.

Reply 4: Thanks for the good suggestion. We reviewed the records, and then added and analyzed the age at surgery, age of onset and course of disease between groups. It was found that the age of onset in MA Group was significantly smaller than the age in WoMA Group (P <0.05). The revisions were made in the text and highlighted in red. (Line 189-196) and Table 4

Changes in the text: *The average age at surgery was 37.1 years (from 20 to 53 years)*

in MA Group and 41.6 years (from 26 to 62 years) in WoMA Group. The average age of onset was 7.9 years (from 4 to 13 years) in MA Group and 23.6 years (from 10 to 56 years) in WoMA Group. The average course of disease was 29.4 years (from 10 to 49 years) in MA Group and 18 years (from 3 to 40 years) in WoMA Group. There was no difference of the age at surgery and course of disease between the two groups. The age of onset in MA Group was significantly smaller than the age in WoMA Group ($P < 0.05$). (Line 189-196)

Please check the highlighted in red in Table 4 as follows:

Table 4 Information of the TMJ ankylosis patients treated by total TMJ prosthesis

No.	Gender	Age at surgery (year)	Age of onset (year)	Course of disease (year)	Group	Sides*	Combined Procedures**	Follow up (month)
1	Male	41	13	28	MA	Bi	A+B	7
2	Male	59	56	3	WoMA	Bi	/	27
3	Female	32	8	24	MA	Bi	A+B+D	5
4	Male	43	9	34	MA	Bi	A+B+D	9
5	Female	52	32	20	WoMA	Bi	A	3
6	Female	39	10	29	WoMA	Uni	D	8
7	Female	62	22	40	WoMA	Uni	/	3
8	Female	25	10	15	WoMA	Uni	A+B+C+D	5
9	Female	48	7	41	MA	Uni	A+C+D	3

10	Female	20	10	10	MA	Uni	B+C	13
11	Female	53	4	49	MA	Uni	A+B+C+D	8
12	Female	23	4	20	MA	Uni	B+C+D	3
13	Female	27	13	14	WoMA	Uni	B+C+D	3
14	Male	27	22	5	WoMA	Uni	A	3

*: Bi=bilateral, Uni=unilateral

** : A, coronoidotomy; B, LeFort I osteotomy; C, SSRO on the opposite side; D, genioplasty

Comment 5: Both SNA and SNB angles in the MA group are severely low before the treatment, is there any bias in the sample selection?

Reply 5: In this study, the most important inclusion criteria were the TMJA patients who underwent unilateral/bilateral TMJ reconstruction with total TMJ prostheses. All the included patients were divided into two groups based on whether the MA was performed. We aimed to investigate the correlation of MA and changes of upper airway. According to the measurements of maxillofacial hard tissue, there were significant difference of SNA and SNB between MA and WoMA group. And this was another reason why the patients in MA group chose to improve the mandibular retrusion deformity.

Comment 6: Table 1 - Gnathion with the capital letter.

Reply 6: Thanks for the reviewer's careful review. The mistake was corrected.

Changes in the text: Table 1 – gnathion: Gnathion

Comment 7: In the introduction section, you talk about growth. Were these patients affected by ankylosis during the growth period?

Reply 7: As replied in Comment 4, we added and analyzed the age at surgery, age of onset and course of disease between groups. It was found that the age of onset in MA Group (7.9 years) was significantly smaller than the age in WoMA Group (23.6 years) (P<0.05). It was a demonstration that micrognathia might occur in patients with TMJA during growing age. The revisions were made in the text and highlighted in red. (Line 262-264)

Changes in the text: *Moreover, the age of onset in MA Group (7.9 years) was significantly smaller than the age in WoMA Group (23.6 years). It was a demonstration that micrognathia might occur during growing age.*

Comment 8: Do these patients suffer from OSAS?

Reply 8: According to the records of patients, there were 5/7 patients in MA Group and 4/7 patients in WoMA Group with complains of sleeping apnea or snoring. But they did not undergo polysomnography before or after surgery. This is another limitation of this study. We put it in the limitations. (Line 345-346)

Changes in the text: *Fourth, according to the records, there were some patients with complains of sleeping apnea or snoring. But they did not undergo polysomnography before or after surgery.*

Comment 9: In the results sections, no significant changes have been obtained neither in the MA group nor in the control group about the hypopharyngeal spaces, I would add some comment about that in the discussion.

Reply 9: Thank you for your suggestion. We added some comments regarding this in the discussion part. (Line 314-321)

Changes in the text: *Though there was no significant change neither in the MA group nor in the WoMA group about the epiglottic region, however, the V3 (T2-T1) and SD3 (T2-T1) significantly increased with MA. These results about the epiglottic region were in agreement with Kim et al's study(16). In Zinser et al's study (11), the volume, length, CSA and SD of the epiglottic region increased significantly after MA and CCWR. As mentioned before, the average change of MA was greater in Zinser et al's study (11.84 mm) (11) than in our study (9.29 mm). And this might explain why the change of the epiglottic region was insignificant in the current study.*

Comment 10: A significant increase in the palatopharyngeal spaces has been obtained in both groups. I would better highlight this point in the discussion. The conclusions are not pertinent to the results if we consider the limitations of the study.

Reply 10: Some comments about palatopharyngeal spaces have been added. And we revised the conclusions. The revisions were made in the text and highlighted in red as follows:

Changes in the text:

In this study, the changes of the upper airway in MA Group were significant. In

WoMA Group, the palatopharynx was the only individual segment of the upper airway that had significant changes. It indicated that the palatopharynx (SAI, VI and SDI) could expanded whether with MA or not. But VI could increase much greater after MA. It was an interesting finding that releasing ankylosis combined TMJ reconstruction alone could obtained an enlarged palatopharynx. In the study of patients with unilateral TMJA undergoing condylar reconstruction with the autogenous coronoid process graft (12), the SD of palatopharynx increased after operation without MA. The results above were in coincidence with our study. (Line 270-278)

In conclusion, release of TMJ ankylosis and condylar reconstruction using total joint prostheses could significantly improve the total volume and other various parameters of the upper airway with MA, while, only the dimension of palatopharynx increased in case without MA. (Line 351-354)

Reviewer E:

Comment 1: In the Abstract, insert P values when comparisons between groups are cited.

Reply 1: The P values have been inserted in the Abstract.

Changes in the text: The changes of Point B (P <0.01), Y-axis angle (P <0.01), SNB (P <0.01), and ANB (P <0.01) were significantly greater in MA Group than in WoMA Group. (Line 55-57)

Comment 2: In Methods, line 124, complete the data on the manufacturer of the prosthesis, such as city, state and country. Also, in line 127, replace "..., and bone grafting, ..." with "..., and previous bone grafting, ...".

Reply 2: The manufacturer information of the prosthesis has been completed.

Changes in the text: All patients underwent bilateral/unilateral condylar reconstruction with Biomet standard prosthesis (Biomet, Warsaw, Indiana, USA).

(Line 123-124)

..., in addition to guiding a precise prosthesis (Biomet, Warsaw, Indiana, USA) placement. (Line 128-129)

Comment 3: In Results, mention whether patients in the MA group reported any improvement in breathing or obstructive sleep apnea.

Reply 3: Thanks for the reviewer's kind suggestion. The lack of data about breathing or obstructive sleep apnea was a limitation of this study. So, we put this in the **paragraph of limitation** in the end of **Discussion**.

Changes in the text: Fourth, according to the records, there were some patients with complains of sleeping apnea or snoring. But they did not undergo polysomnography before or after surgery, and it was not available whether breathing or obstructive sleep apnea had been improved. (Line 354-357)

Comment 4: Complete the headings in Tables 5 and 6, adding: "...according to the groups and the significance of the comparisons between T1 and T2."

Reply 4: The headings in Tables 5 and 6 have been revised.

Changes in the text: Table 5 The measurements of maxillofacial hard tissue

according to the groups and the significance of the comparisons between T1 and T2

(in Tables - revised.docx)

Table 6 The measurements of upper airway according to the groups and the significance

of the comparisons between T1 and T2 (in Tables - revised.docx)