

Dear Editor,

We feel very happy to receive the news that all the two reviewers are satisfied with our work. This paper has been revised accordingly based on these comments. We strongly believe that these modifications will greatly improve the quality of our manuscript. We hope that you find our responses satisfactory and the manuscript is now acceptable for publication. Major edits are highlighted within the paper.

Reviewer #1:

1. The novelty of the study is questionable.

Response: Thank you for your valuable comments. Early immediate implants were mainly concentrated on single-rooted anterior teeth and premolars with flat roots. With the development of clinical implant technology and oral implant materials, the clinical research of immediate implant placement of molars has attracted much attention in recent years. It has been reported that there is no statistically significant difference in the success rate between immediate implant placement and delayed implant placement in the molar area without inflammation [1-3]. However, in clinical practice, a large number of mandibular molars cannot be preserved due to severe chronic apical inflammatory lesions. Due to the complex shape of tooth sockets after tooth extraction, periodontal soft tissue and alveolar bone are severely damaged, and a large number of inflammatory granulation tissues exist, which adversely affects the success rate of immediate implant surgery. For this reason, Most physicians consider molars with chronic apical periodontitis lesions as contraindications for immediate implant placement. At the request of the patient, we tried to immediate implant placement of mandibular molars with chronic apical periodontitis in clinical work. In this study, we screened and analyzed the immediate implantation cases of mandibular molars with chronic periapical inflammation in our group in recent years. The clinical effect was evaluated by comparing the soft and hard tissue of the patients 5 years after implantation.

[1] Yuan X, et al. Biomechanics of Immediate Postextraction Implant Osseointegration. J Dent Res. 2018 Aug;97(9):987-94.

[2] Ragucci GM, et al. Immediate implant placement in molar extraction sockets: a systematic review and meta-analysis. Int J Implant Dent. 2020 Oct 13;6(1):40.

[3] Kusuyama J, et al. Low-intensity pulsed ultrasound promotes bone morphogenic protein 9-induced osteogenesis and suppresses inhibitory effects of inflammatory cytokines on cellular responses via Rho-associated kinase 1 in human periodontal ligament fibroblasts [J]. J Cell Biochem, 2019, 120(9): 14657-69.

Reviewer #2:

The authors do not indicate what the novelty of this study consists of. In particular, the study does not contain new concepts, hypotheses, and/or mechanistic, diagnostic, or therapeutic information. This should be reviewed and clarified in the manuscript. In general, the manuscript should be presented in a more coherent and organized manner.

Response: Thank you for your valuable comments. We are sorry that we did not clearly state the innovation of this study. The innovation of this research can be roughly divided into two aspects. On the one hand, we performed immediate implantation of mandibular molars with chronic

inflammatory periapical periodontitis and conducted a retrospective study of these cases after 5 years of crown restoration. On the other hand, we quantitatively studied the changes of bone mass and bone mass around the implant by using Simplant software and Image J software. According to your suggestions, we have added the innovative and relevant content of this study in the preface of the article.

Specific comments are detailed below:

1. Title: the title does not reflect the main subject/hypothesis of the manuscript. The authors essentially compare two groups. This should be clear in the title.

Response: Thank you for your valuable advice. According to your suggestion, we believe that the two groups in the study should indeed be reflected in the title. Therefore, we changed the title to: “Comparison of five-year outcomes of immediate implant placement for mandibular molars with chronic apical periodontitis and those without obvious inflammation: a retrospective study”.

2. Abstract: The objective should state that two groups are being compared. The outcome variables studied should also be detailed. In the methods, it should be noted how, when and in what way these variables were evaluated. In the results, the findings obtained when comparing these variables in the groups should be presented, and finally, in the conclusions, the findings found in these variables when comparing the groups should be described.

Response: According to your suggestion, we have revised the summary. The revised content is as follows:

“BACKGROUND: Most physicians consider molars with chronic apical inflammatory (CAP) lesions as contraindications for immediate implant placement. At the request of the patient, we tried to implant mandibular molars with chronic periapical periodontitis immediately in clinical work.

AIM: The aim of this study was to retrospectively analyze and compare the 5-year outcomes of immediate implant placement of mandibular molars with CAP and those without obvious inflammation.

METHODS: The clinical data of patients with immediate implant placement of mandibular molars in the Department of Oral and Maxillofacial Surgery, the Affiliated Hospital of Qingdao University from June 2015 to June 2017 were collected. The patients were divided into CAP group (n = 52) and No-CAP group (n = 45). The changes of bone mineral density and bone mass around implants were analyzed 5 years after implant restoration.

RESULTS: At 5 years after implantation, the peri-implant bone mineral density was 528.2 ± 78.8 Hounsfield (HU) in the CAP group and 562.6 ± 82.9 HU in the No-CAP group ($P = 0.126$). There was no statistically significant difference in marginal bone resorption around implants between the two groups, including buccal ($P = 0.268$) and lingual ($P = 0.526$) in the vertical direction and buccal ($P = 0.428$) and lingual ($P = 0.560$) in the horizontal direction. There was no statistically significant difference in the changes in the peri-implant jump space between the two groups, including the buccal ($P = 0.247$) and lingual ($P = 0.604$) in the vertical direction and the buccal ($P = 0.527$) and lingual ($P = 0.707$) in the horizontal direction. The gray value of Cone-beam computed tomography (CBCT) measured by Image J software can reflect the bone mineral density. In the CAP area, the gray values of the bone tissue immediately and 5 years after implant placement differed significantly from those of the surrounding bone tissue ($P < 0.01$).

CONCLUSION: The results of this study suggest that immediate implant placement of the mandibular molars with CAP can achieve satisfactory 5-year clinical results, without significant differences in the complications, survival rate, or bone tissue condition from No-CAP mandibular molars.”

3. Line 6. The CAP group is described as an experimental group. This makes it appear that it is a clinical trial. It is recommended to treat it as a CAP group and the comparison group as a No CAP group. This should be corrected throughout the manuscript.

Response: Thank you for your valuable comments. Based on your comments, we have revised the grouping names throughout the manuscript. We changed the name of the experimental group to the CAP group and the control group to the No-CAP group.

4. Line 10. Define HU. Lines 9-11. At the end of the sentence, simply include the p-value in parentheses. Therefore, you avoid writing continuous sentence.

Response: We are in full agreement with your proposal. We redefined HU and supplemented the full name of HU (Hounsfield). In addition, we added P-values to the sentences describing the results of the evaluation indicators to make the findings more rigorous in the abstract.

5. Lines 12-13. Please present the values of marginal bone resorption and jump gap with p-values in parentheses. Moreover, please define gray values. It should be noted that the conclusions are based on the limitations of the study.

Response: At your suggestion, we have added P-values for marginal bone resorption and jump gap in the abstract. In addition, we explain the measurement and significance of gray values. In addition, according to your suggestion, we have revised the conclusion of the abstract accordingly.

6. Key Words: the keywords reflect the focus of the manuscript; however, most of them are not MeSH terms.

Response: Thank you for your valuable advice. We selected six of the MeSH terms that were most relevant to this study as the keywords of this article based on the content of this study. So that readers can search this article according to the keywords. The revised six keywords are: Molar; Chronic apical periodontitis; Dental implantation; Retrospective study; Bone density; Treatment outcome.

7. Background: the manuscript adequately describes the background, and presents the status and significance of the study; however, some adjustments need to be made: Lines 10-13. Add references. Lines 17-20. Add references. Lines 29-30. Add more references. Lines 32-33. Add references. Line 34. Add references. Page 4. Line 4. Add references. Page 4. Line 7. Add references. Page 4. Line 8. Add the reference of Alsaadi et al. Page 4. Line 11. Add reference. Page 4. Lines 13-15. Different types of study are indicated but you only present a study carried out on animals. Page 4. Lines 15-16. The comment about your group is not necessary. Page 4. Lines 17-24. This paragraph is part of the methodology. It should be removed from the introduction.

Response: We particularly appreciate your careful and rigorous approach to the article. According to your suggestion, we have supplemented and revised the literature in the background of the article.

8. The authors must indicate the novelty of this study. The objective should be adjusted considering the recommendations given above.

Response: Thank you for your advice. We supplement the innovation of this study in the later part of the background. In addition, we adjusted our research objectives according to your suggestions.

9. The study does not indicate anything about the evaluation of patient satisfaction (line 26). How was it evaluated? Lines 27-28. This comment is unnecessary.

Response: Thank you for your careful review of our article. We did conduct a questionnaire survey on patient satisfaction during the course of this study, which was quite extensive and complicated. Patient satisfaction surveys are not presented to readers in this article because of word and picture limitations in this article. Therefore, we deleted the terms related to patient satisfaction in the article and will publish them in future articles. In addition, we have removed Lines 27-28 as you suggested.

10. Methods: Line 5. Some typos must be revised. Line 8. It must be indicated that the Declaration of Helsinki was fulfilled. Line 12. "no relevant". What do you mean? Line 21. Describe this disinfection routine in detail. Lines 25-26. This procedure should be described in more detail. Was a prosthetically guided protocol used? Please comment on this. Page 6. Line 2. "Cone-beam computed tomography". Present the acronym in parentheses. Was CBCT used before implant placement? Was it part of the protocol?

Response: Thank you for your valuable advice. According to your suggestion, we have revised the corresponding content.

Line 8. "This study was conducted in accordance with Declaration of Helsinki guidelines and regulations, and all study methods were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYKYL958311920)."

Line 12. By "no relevant" here, we want to express that we routinely screen patients before implant surgery, and patients cannot have systemic diseases and take related drugs. It is impossible to predict whether systemic diseases and drugs will affect the osseointegration of the implants in such patients undergoing immediate implant surgery. We changed this section to: "no systemic disease and the use of related drugs".

Line 21. We are very sorry that we thought a detailed description of disinfection would add space to the article. Therefore, the importance of this part is ignored. According to your suggestion, we have completed this part. "We used 1% iodophor for disinfection and asked the patient to gargle for 20 seconds before sterilizing the maxillofacial area, up to the palpebral fissure, down to the level of the hyoid bone, and left and right to the front of the tragus."

Lines 25-26. For this study, how to remove the inflammatory tissue is the key step to determine the clinical effect during the immediate implant surgery. Therefore, we have supplemented this part of the article. "The inflammatory tissue on the edge and inside of the mucoperiosteal flap was pruned, and the inflammatory tissue attached to the inner wall of the alveolar fossa was scraped with an appropriate type of scraping spoon and scovel, and then polished with large, medium, and small ball drills until there was no fibrous tissue on the bone wall of the alveolar fossa."

Page 6. Line 2. Following your suggestion, we have added the acronym "Cone-beam computed tomography (CBCT)". Before implant surgery, in order to more accurately judge the condition of

the affected tooth itself and the surrounding tissues and select the appropriate type of implants, we routinely perform CBCT examination before surgery, and the patient's consent is obtained before the examination.

11. Page 6. Line 12. The result of the intra and inter-examiner calibration must be presented.

Response: Thank you for your valuable advice. According to your suggestion, we test the difference of the observation results of the three observers by intraclass correlation coefficient (ICC). According to the specificity of the evaluation indicators in this study, the "peri-implant bone mineral density" with the most complicated detection steps was selected for ICC calculation, which could reflect the differences in the observation results of the three observers in this study. The "peri-implant bone mineral density values" measured by three observers in this study were tested for inter-observer difference, and the calculated ICC value was 0.816, which was between 0.75 and 0.9, indicating a good consistency of the observation results.^[1] We have added the above to the methods and results in the article.

[1] Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016; 15(2): 155-63.

12. In the statistical analysis, the variables that had a normal distribution and those that did not should be presented. The primary and secondary outcome variables should be clearly defined.

Response: We fully agree with the suggestion that we do not explain the statistical analysis part clearly. Therefore, we modified the statistical analysis section as follows.

“ICC calculations and statistical tests were performed using SPSS 20.0 (IBM, Chicago, IL). The age of the patients belonged to non-normal distribution data, and the Wilcoxon Signed Rank Test was used for analysis. The data of peri-implant bone tissue changes (bone mineral density, marginal bone loss, jump gap, gray value) belonged to normal distribution data and were analyzed by independent sample t-test. For the gender of patients, Chi-square test was used to analyze them. A P-value < 0.05 was considered to indicate statistical significance.”

13. Figure 2. It is full of typos. “endoscopy”? Please revise. A preoperative radiograph is essential. The images should detail only the operating area. In figure E, the white space around the removed elements should be eliminated.

Response: According to your comments, we have modified the typo in the legend of Figure 2 (Changed to Figure 3) and added the preoperative CBCT image of this patient (Figure 2). In addition, we reduced the white space around the removed elements.

14. Figure 3. Define MBD and gray.

Response: Based on your suggestion, we have revised the legend (Changed to Figure 4) to make this part more understandable to readers.

“Fig. 4 Method for measuring changes in bone tissue around implants. A. The peri-implant bone mineral density was measured by Simplant software. B. Schemas of marginal bone resorption and jump gap measurements. L0 is the long axis of the implant, L1 is perpendicular to L0, H1 is the vertical distance from the crest of the alveolar bone to L1, W1 is the horizontal distance from the most lateral side of the alveolar bone wall to the edge of the implant, H2 is the vertical distance from the highest point of contact between the implant and bone to L1, and W2 is the width of the

jump gap. C. Image J software was used to measure the gray value of the bone destruction area at the root apex of the affected tooth (The gray value of alveolar bone CBCT can reflect its bone mineral density).”

15. Results: Table 1 was not presented. It is essential that the comparison of all the baseline characteristics of the patients that made up the two groups be presented in a table. Define HU.

Response: Thank you for your constructive comments. In Result 2, we describe the relevant data in detail in the manuscript without the need for tabular presentation. Table 1 is our writing error, please forgive me. In accordance with your comments, we present the basic information of the two groups of patients in the form of tables at the beginning of the results (Tables 1 and 2). We redefined HU and supplemented the full name of HU (Hounsfield).

16. Figure 4. p-values must be presented. “...and 32.5 ± 15.3 5 years after implant restoration, with no significant differences between the two groups ($p < 0.01$)”. It is indicated that there were no differences, but the p-value indicates that there were.

Response: Thank you for your valuable comments. According to your comments, we have modified the legend of Figure 4 (Changed to Figure 5) and added the *P*-value. In addition, the result 3 of the article has also been modified according to your comments.

“Fig. 4 Changes in bone tissue around implants. A. Vertical edge bone absorption of peri-implant (Buccal $P = 0.268$, Lingual $P = 0.526$). B. Horizontal edge bone absorption of peri-implant (Buccal $P = 0.428$, Lingual $P = 0.560$). C. Implant-bone contact peak increment (Buccal $P = 0.247$, Lingual $P = 0.604$). D. The change in the jump gap (Buccal $P = 0.527$, Lingual $P = 0.707$).”
“The inflammatory bone destruction area of the alveolar bone in the CAP group disappeared 5 years after implant denture restoration. The gray value difference between the CAP lesion area and the surrounding bone tissue was 107.6 ± 21.7 immediately after surgery and 32.5 ± 15.3 5 years after implant restoration, with significant differences between the two groups ($P < 0.01$).”

17. Discussion. The information in the first paragraph has already been sufficiently presented. As in the introduction, many concepts are not supported by bibliographical references. “The present study involved no bone grafting in the jumping gap in the CAP or NC group”. Contrast with other studies that do use it. *Porphyromonas* should be in italics. The discussion is very poor. The results should be contrasted with previous studies in a more detailed way. The many limitations of this study should be described.

Response: Thank you for your decisive advice. According to your suggestion, we have supplemented the corresponding references in the discussion and added some content. None of the patients in this study underwent bone grafting during surgery. A review of the literature found that the jump gap after immediate implantation can heal itself like the extraction socket.^[1] The research purpose of this study does not involve the related research of bone grafting. Whether the healing of jump gap can be accelerated after bone grafting will be carried out in the follow-up study. In the later part of the discussion, we detail the limitations of this study and future research plans.

[1] Naji BM, Abdelsameaa SS, Alqutaibi AY, Said Ahmed WM. Immediate dental implant placement with a horizontal gap more than two millimetres: a randomized clinical trial. *Int J Oral Maxillofac Surg.* May 2021;50(5):683-690.

18. Conclusions: It should be noted that the conclusions are based on the limitations of the study.

Response: Thank you for reminding us that we carefully analyzed the limitations of this study and added them in the later part of the manuscript.

“At the same time, this study also has some limitations. This study is a retrospective study, the credibility of the findings is weaker, and strict inclusion and exclusion criteria were set in this study to minimize variables that are not relevant to the purpose of the study. The research sample of this study is small and cannot accurately represent the situation of the sample population. The study cases were all patients with good compliance, which caused a certain selection bias in this study. In the future, we will conduct a prospective study corresponding to this study to expand the sample size and follow-up time, and further explore the soft and hard tissue conditions of immediate dental implantation in mandibular molars with chronic apical periodontitis.”