Author’s response to reviews

Title: Efficacy of nano-carbonate apatite dentifrice in relief from dentin hypersensitivity following non-surgical periodontal therapy: A randomized controlled trial

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Author’s response to reviews:

Responses to editor

Comment #1:
specify in the Ethics approval and consent to participate section whether the consent was written or verbal.
Authors’ response:
The Ethics approval and consent were achieved in written version. It has been specified in the manuscript as follows: “Each participant was fully informed about the research and signed the written consent prior to enrollment.” (see in Methods section, line 16, page 6)

Comment #2:
too much potentially identifiable information in the Additional Table
Authors’ response:
Thank you very much for pointing it out. We have changed the ages to age ranges and the gender information has been removed (see in Table S1).

Comment #3:
add a section "Additional files" (after the References/Figure legends) where you list the following information for each additional/supplementary file in the file inventory:
- File name (e.g. Additional file 1)
- Title of data
- Description of data
Authors’ response:
We have added the section of "Additional files" (see in line 11-12, page 23).

Responses to reviewers

To reviewer 1:
Thank you very much for your kind comment.

To reviewer 2:
Thank you very much for your meticulous report. According to your constructive comments, we realized that the results need to be interpreted with more caution, so we have made extensive modifications in the original manuscript, especially in the Discussion section. Here, we attached the revised manuscript for your approval. A document replying to every comment was also summarized and enclosed. If you have any further questions, please contact us without hesitation.

Comment #1:
There are a few typographical/grammatical/use of English errors that would need to be sorted out before publication.

Authors’ response:
The spelling and syntax errors have been checked and corrected. We have minimized typographical, grammatical and bibliographical errors in the revised manuscript.

Comment #2:
the primary outcome does not appear to have been achieved and this is not clear in the manuscript.
In fact, the primary outcome for the study is not formally stated. In the CONSORT statement, it is specified to be presented on p8-9, but the only mention is on p7, where the 'main outcome' is noted. Taking this as the primary outcome, it needs to be made clear in the abstract and discussion that it was not achieved to the 5% significance level. This means other secondary analyses need to be interpreted with care. The abstract and discussion needs to be re-worked to be transparent about this situation. For instance, I do not think the statement from p13: 'During the following 6 weeks, the degree of tooth sensitivity went significantly lower in the test group than that in the control group' can be supported. The finding of a benefit for the test product in Schiff at 6 weeks should be couched in terms of 'some evidence' of efficacy.

Authors’ response:
In this RCT, we use the result of air-blast test as primary outcome. To be more specific, change of VAS and change of Schiff were considered as primary outcomes in this study. We didn’t perform tactile test or cold water test (reasons see Response of comment #7), so there weren’t secondary outcomes in our study. To make it clearer, we have stated in the revised manuscript as follows: Primary outcomes were change of VAS and change of Schiff at all evaluation stages. (see in Methods section, line 1-2, page 11)
The results have been interpreted with more caution in the Abstract, Results and Discussion section. The main changes were listed as follows:

1. The results of 6-week evaluation have been added in the Abstract-Result part: “The 6-week results showed borderline significance between groups in terms of change of Schiff (p = 0.027) and no significance in terms of change of VAS (p = 0.256).” (see in Abstract section, line 22-24, page 2)

Also, this result was more transparent in the Result section: “However, after 6 weeks, there was no significance between groups in terms of change of VAS (p = 0.256).” (see in Results section, line 2-3, page 12)

2. The conclusion has been revised into:
“Home-use of n-CAP-based dentifrice had some benefit on alleviation of DH following non-surgical periodontal therapy after 4 weeks compared to the control product.” (see in Abstract section, line 1-3, page 3).

“Within all the limitations, this randomized controlled trial showed that the application of n-CAP-based dentifrice had some benefit on the reduction of DH after 4-week at-home use compared to the control dentifrice.” (see in Conclusion section, line 22-24, page 15)

3. In the first paragraph of Discussion, the 6-week results have been underlined as follows: “The 6-week comparison between group only showed borderline significance.” (see in Discussion section, line 16-17, page 12) In addition, the possible reason was explained in the fifth paragraph of the Discussion part. (see in Discussion section, line 1-8, page 14)

Comment #3:
The study does seem small for this type of investigation. It appears the authors had an over-optimistic estimate of the effectiveness of the treatment relative to the control. The actual vs expected difference should be commented on more clearly in the discussion, which lacks a section on the time-course of the product differences (see 13. below).

Authors’ response:
Yes, we need to be more conservative when interpreting the results, so the main corresponding modifications have been listed in the Response of Comment #2.

As for the time-course effects of the product, it has been reorganized in the revised Discussion section. To be more specific, in the third paragraph of the Discussion section (see in line 1-14, page 13), we explored the instant effect and the possible reason. In the next paragraph (see in line 15-25, page 13), the results of the 4-week comparison and the underlying mechanism. Then the fifth paragraph (see in line 1-8, page 14) explored the reason why 6-week comparison did not show further significance.

Comment #4:
Relatedly, the starting Schiff scores seem quite low versus other recent studies, leaving a small margin for improvement. This should be stated as a limitation of the study. Really, these points all tie together: small study + small difference due to treatment = poor resolution of a potentially efficacious treatment from the control.

Authors’ response:
The limitation of relatively low DH baseline has been added as follows: “Moreover, the relatively low DH level at baseline left a limited extent for improvement. Hence, clinical trials enrolling a larger number of patients with higher inclusion criteria of baseline DH are
encouraged to confirm the present findings and determine whether this product could be recommended to the general population.” (see in Discussion section, line 15-19, page 15)

Comment #5:
Also, the authors state those with higher sensitivity at start experienced more benefit, but this is not shown in any of the tables. The supporting data for the statement needs to be shown in a table.
Authors’ response:
This finding still lacked enough evidence in this study, so we have removed it (see in Discussion section, page 13).

Comment #6:
The introduction should provide clearer explanation of proposed mode of action: is it binding and blocking tubule openings, or serving as a locus for mineralisation? This relates to the time expected to be taken for an effect to be observed.
Authors’ response:
The introduction of the nano-particles-based products has been reorganized as follows: “Some studies have revealed that nano-sized particles would adhere to the dentine surface increasingly because of high surface energy, indicating their potential for occluding tubules [14, 15]. More importantly, the remineralization potential of nano-sized particles enabled them to maintain continuous capacity for exposed surface repair [14, 16, 17].” (see in Background section, line 11-15, page 5). Correspondingly, in the Discussion section, we related the potential for dentine tubules blocking with post-polishing evaluation results and remineralization with the 4-week results (see in Discussion section, line 1-25, page 31).

Comment #7:
The quoted 'Holland' reference advises that two independent assessment techniques are used for sensitivity studies, typically air-blast and tactile. The rationale for only using one should be provided; and acknowledgement in discussion that further studies should include second assessment technique (plus larger sample size)
Authors’ response:
The rationale has been stated more clearly in the revised manuscript as follows: “Air-blast test was used to test hypersensitivity in this study because it caused more frequent pain than the tactile stimuli and involved a wider area of dentine, which indicated that the air-blast test is a sensitive and reliable method to detecting the degree of hypersensitivity [33]. The air-blast stimulus could better mimic the practical situation, since patients experienced sensitivity from cold water, food or air more frequently than other stimuli. In addition, many studies showed correlation between the results of air-blast test and tactile test [29, 34-36].” (see in Discussion section, line 20-25 on page 14 and line 1 on page 15). Furthermore, secondary outcomes should be encouraged in the following studies to provide more supporting evidence, and we added the statement as follows: “It is recommended that at least two independent stimuli should be applied [37], so secondary outcomes such as tactile, cold water test or subjective questionnaire could provide more supporting evidence in assessing DH degree”. (see in Discussion section, line 1-4, page 15)
Comment #8:
P-values quoted in abstract and discussion should be based on comparison of mean changes from baseline to a certain timepoint, not comparison of actual mean values at that time point (as currently). As an example, p-value for 4-week VAS should be p=0.036, not p=0.005.
Authors’ response:
As stated in the response of Comment #2, change of VAS and change of Schiff at all evaluation stages were considered as primary outcomes. The P-value mentioned has been changed accordingly. In the Abstract section, it has been changed as follows: “for change of VAS, test group: 2.27 ± 2.47 versus control group: 1.68 ± 2.24, p = 0.036; for change of Schiff, test group: 0.94 ± 0.92 versus control group: 0.61 ± 0.83, p < 0.001”. (see in Abstract section, line 20-22, page 2)

Comment #9:
Presence of fluoride in toothpastes? Did either of the toothpastes contain fluoride? If so, how much and in what form?
Authors’ response:
Both the toothpaste in this study do not contain any form of fluoride. The relative statement has been added to the manuscript as follows: “Both of the dentifrices were without any form of fluoride.” (see in Methods section, line 14-15, page 9)

Comment #10:
How was assessor trained? Was any reproducibility measure used during the study?
Authors’ response:
There was only one examiner in this RCT, who had more than 5-year experience of dental practice. Before the start of this study, a preliminary training was provided within 8 voluntary participants to receive air-blast tests and periodontal assessment. After the training, the same procedure as employed at baseline was used as the standardized method throughout the clinical trial. Revised part can be seen in Methods section, line 2-4, page 10.

Comment #11:
Were covariates used for statistical analysis? Please specify.
Authors’ response:
The covariates were the corresponding VAS of Schiff score at baseline. We have specified it as follows: “The corresponding baseline results of VAS or Schiff score were covariates.” (see in Methods section, line 23-24, page 10)

Comment #12:
There is a repeated point on p12 regarding 'Significant decrease in VAS and Schiff scores were detected after in-office application, whereas no difference in the degree of DH was observed between groups'. Only need to state this once.
Authors’ response:
We have removed the repeated statement (see in Discussion section, page 13).

Comment #13:
Study is small (see point 3) so differences in degree of difference at different timepoints should not be over-interpreted. However, the fact that the between-product changes from baseline at 4-
weeks were significant, but fell short of significance at 6 weeks (for VAS), and were only of borderline significance for Schiff, needs some comment. Authors should comment on potential reasons why the placebo group continued to improve during the course of the study in their discussion on the lack of efficacy by VAS at the primary time-point.

Authors’ response:
The reason why 6-week results only showed borderline significance for Schiff has been added as follows: “Interestingly, 6-week comparison between groups did not showed further significance than that of 4-week evaluation, raising the question whether 4-week results in the test group has decreased to a low DH level, leaving a minimal margin for further relief. As original data showed, there were as much as 93.1% patients in test group had Schiff score ≤ 1 after 4-week home-use. It was also implied in the tendency from 4-week to 6-week of Figure 2 where a flatter line stood between these two timepoints. As a consequence, DH level went lower consistently in the control group while limited improvement occurred in the test group after 4 weeks.” (see in Discussion section, line 1-8, page 14)

As for the reason why the placebo group continued to improve, apart from the placebo effect and Hawthorne effect which have been mentioned in the original manuscript (see in Discussion section, line 9-16, page 13), another possible reason might be that DH tend to self-heal over time after non-surgical periodontal therapy (see in Discussion section, line 16-19, page 13).

To reviewer 3:
We are very grateful for your comments on the manuscript. According to your constructive suggestions, we amended the relevant part of the manuscript. Your questions were answered below:

Comment #1:
In the abstract, background, in this part, the first sentence is important to indicate the research gap for the present study. Therefore, please elucidate the research gap for the background.

Authors’ response:
Thank you for pointing out this. We have made it clearer in the first sentence in the background in Abstract section as follow: “Dentine hypersensitivity (DH) could occur or intensify after non-surgical periodontal therapy because of the exposure of dentine tubules, but currently no gold standard exists to treat DH.” (see in Abstract section, line 5, page 2)

Comment #2:
In the data analysis, authors stated that "the normality of data was assessed by Shapiro-Wilk test. Data with skewness was converted before analysis." Please report methods of the data transform detaily.

Authors’ response:
We used logarithmic conversion to transform the data with skewness. To make it more clear, we have revised the statement as follows: “Data with skewness was converted through logarithmic conversion before analysis” (see in Methods section, line 19, page 10).
Comment #3:
In the data analysis, since the mixed linear model was adopted, and two level is the person level and tooth level, the tables present in the study did not report the results with two level. Please revised.
Authors’ response:
When the mixed linear model was applied, it does not necessarily mean the results of different levels need to be reported. For example, in Tonetti’s study, the result of multilevel analyses only presents the tooth-level results rather than the centre-level and patient-level results (Table 4 in their paper). In our model, we use patient number as “subject”, which was regarded as the first level. Then, their teeth were regarded as the second level.

Reference: