Author's response to reviews

Title: Histological evaluation of the efficiency of low-level laser therapy on bone regeneration in extraction sockets grafted with allograft material covered with resorbable collagen dressing

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Response to Reviewers

Reviewer: Siddharth Shanbhag

1. What was the most common reason for tooth extraction? Especially since the inclusion criteria required all 5 socket walls to be intact. Also, include this point in the discussion since the results of the study only relate to 'ideal' sockets and not necessarily in sockets with 1 or more missing/damaged walls, which is very often the case.

The most common reasons for tooth extraction were: coronal fracture, profound decay, tooth mobility which do not damage the wall socket after extraction.
Since our paper is a preliminary study, we included only ‘ideal’ socket. Further studies, with different clinical aspects of the walls are necessary.

2. Describe the device or method. How was the LLLT delivered?

LLLT was started after removal of the suture. The irradiation protocol was included in our manuscript: an OsseoPulse AR300 at an intensity of 20mW/cm² was used for 20 minutes per day, for 21 consecutive days. The LLLT was delivery by operators.
The compliance was assessed at each visit.

3. Were there any ‘drop-outs’ i.e. did some patients who were initially included, have to be excluded following the extraction?

After extraction, two patients with a missing wall caused by infection or surgical trauma and three patients with immediate complications after grafting such as loose membrane, loose bone graft material were 'drop-outs' from the study (As described in paragraphs 78-86).

4. How was the randomization performed?

We used block randomization. This method ensures equal treatment within each block.

5. It is very important to know how the biopsy times were determined. Authors state “If a site could be biopsied without compromising the long term success of the dental implant, the biopsy was carried out…” How was it determined whether a biopsy could or could not be performed i.e. how was 'healing' within the sockets assessed? (e.g. radiographically?)

The biopsy time were determined radiologically.

6. Why was quantitative histomorphometry (e.g. % bone area, % new bone formation, % residual graft) not performed? Can 'significant' differences be appreciated based on qualitative histology and can it adequately provide the basis for making clinical recommendations?
As our study is only preliminary and the results were meet expectations we intend to extend the study with histomorphometric assessment.

7. Were histological observations performed in duplicate? Were the observers blinded to the treatment groups? Was it assessed using computerised methods?
We did not use duplicate observations. We used one trained, calibrated and blind to the groups evaluator.

Results:
8. Please provide an initial sentence regarding the general overall outcome i.e. did all 30 patients complete the study?, were there any complications? etc.
We added informations in text.

9. Were there any significant differences in terms of vascularity of the regenerated bone between the groups?
Was there any expected effect of LLLT on angiogenesis?
No significant differences in terms of vascularity of the regenerating bone between the groups was observed.

10. “No evidence of malignancy was observed.” Is there a risk of inducing malignancy with LLLT?
There is no risk of inducing malignancy with LLLT.
We rephrased the sentence.

Discussion:
11. Would it have been useful to include another control group of patients who received only LLLT with no socket grafting? Is there any evidence that LLLT enhances 'de novo' bone healing?
We would like to consider the reviewer’s suggestion to use another control group of patients who only LLLT with no socket graft in a further study.

12. Please provide a reference for “The presence of high amounts of collagen fibres in the test group may represent an early effect of the LLLT on bone repair.”
Also, could this be correlated to some in vitro or preclinical in vivo evidence for an increase in LLLT-induced collagen formation by gene or protein expression?
We added the information in text.

13. It would be of scientific value to discuss the effects of LLLT on various stages of osteogenesis based on the current findings and existing literature. For example, the authors have stated that LLLT may increase osteoblast proliferation and differentiation, while the current findings suggest that it may also improve ECM production, but the effects of LLLT on mineralization (of ECM) may be questionable.
15. Please do not refer to other studies using “his”, “he”, etc.

16. Please include a note on the study limitations and scope for inferring the results to clinical practice. One concern might be that patients need to visit the clinic for 21 days after surgery for LLLT to be delivered adding to time and cost which must be weighed against the proposed benefit of reduction in overall treatment time.

17. Please discuss the findings in light of the current evidence for management of extraction sockets especially ‘in-tact’ (5-wall) sockets. Systematic reviews are available on the topic.

According to the reviewer’s suggestion we added information in the manuscript text.
Reviewer: Guilherme Oliveira

1. The problem with the references continues, at least 11 references were erroneously cited. Some information in the Material and methods sections are missing like the methods to evaluate the vascular structures and osteoblast as the authors exposed in the cover letter. The harvesting of the samples were possible in all the patients?

   We have reconsider the reference categories in the revised manuscript.

2. Finally, I do not understand why the histomorphometric analysis has not been performed. The sample were cut and stained, then there is no reasonable explanation to not perform the histomorphometric analysis that is much more interesting to assess the amount of bone tissue than radiographic analyzes.

   As our study is only preliminary and the results were meet expectations we intend to extend the study with histomorphometric assessment.