Lasers in Medical Science (2019) 34:1261–1263
https://doi.org/10.1007/s10103-019-02743-2

LETTER TO THE EDITOR

Methodological correctness of a recent publication on pain entitled "Evaluating the effect of photobiomodulation with a 940-nm diode laser on post-operative pain in periodontal flap surgery"

Vahid Rakhshan [1,2]

Received: 4 August 2018 / Accepted: 1 February 2019 / Published online: 4 March 2019

Dear editor,

I read with great interest the excellent study of Heidari et al. [1], which was concerned with the efficacy of photobiomodulation in alleviating pain after periodontal surgery. It was a nice split-mouth randomized clinical trial with numerous advantages.

However, I had some questions and suggestions.

1. I would appreciate if the authors can explain how this particular sample size had been determined.
2. The current design looked like a repeated-measures design. So, it would be appropriate to use a repeated-measures ANOVA (or a similar test) instead of paired *t* tests. If it is not possible to conduct an RM-ANOVA now (for example, lack of raw data), at least, the multiple comparison problems should be addressed using methods such as the Bonferroni correction, i.e., by reducing the level of significance from 0.05 to 0.007, and considering any *P* values above 0.007 as non-significant.
3. If the level of significance is to be adjusted to 0.007, it would be needed for the *P* values in Table 2 to be reported up to at least three decimal places; they are currently rounded to two decimal places, which is not common.
4. There can be an error in the conducted paired *t* test. I compared the groups using an ***independent-samples*** *t* test (an unpaired *t* test). I anticipated to see different *P* values from what had been reported in Tables 1 and 2 (supposedly calculated using a paired *t* test), because my test was different from what had been used in the study (i.e., a paired *t* test).

   To my surprise, each and every *P* value calculated by me (using the *un*paired *t* test) was identical to its counterpart *P* value reported in Tables 1 and 2 (and reported to be calculated with a *paired t* test). Only two of the *P* values reported in the article differed subtly with what I calculated using the unpaired test. In one case, the result of paired *t* test (used in the article) had become 0.004, while my calculated *P* value (using the independent-samples *t* test) became 0.003; in another case, the reported *P* was 0.02, while my calculated *P* became 0.0266. The rest of *P* values were all the same to the smallest detail, in spite of using quite different tests.

   To my knowledge, it is technically impossible for paired and unpaired *t* tests to yield the exact same *P* value for a given comparison, when the groups are extremely matched; and we know that a split-mouth design is an ultimate form of matching. So, I think the paired *t* test reported in the study might have some errors; perhaps, an *independent-samples t* test has been mistakenly utilized instead of a paired *t* test that was supposed to be used. This should be double-checked (taking into account that a paired *t* test itself is not the best option and should be replaced by a repeated-measures ANOVA or a similar repeated-measures analysis).
5. I think subjective pain scores are reliable only when patients do not take analgesics; if it was not possible to rule out analgesics, pain scores would be reliable when the analgesic dose remains constant during the study period (and among all the subjects) and does not change based on the pain felt. Obviously, if analgesic dose freely changes to control the pain effectively and address the fluctuations in pain (i.e., when the pain is severer, the patient takes more analgesics), there might remain no considerable pain differences either among individuals or over time. And if any

✉ Vahid Rakhshan
vahid.rakhshan@gmail.com

1 Department of Cognitive Neuroscience, Institute for Cognitive Science Studies, Tehran, Iran

2 Department of Dental Anatomy, Dental Faculty, Azad University, Tehran, Iran

pain differences remain in the end, it is not known how much of the difference is due to the unaccounted changes in analgesic dose.

In this study, patients could consume as many analgesics as necessary (up to three capsules) to keep their pain at a tolerably low level. The greater the surgery pain, the more the taken analgesics. This could simply reduce the pain back to tolerable levels or even to zero. So, basically, the pain they felt was not *only* a function of the surgery trauma (alleviated by laser or placebo) but was *also* a *strong* function of the ***ever-changing*** *dose* of analgesic.

So, I expected their perceived pain (VAS) to be as low as possible throughout the study period (thanks to the painkiller), regardless of the intervention group (sham or laser) and regardless of the day in the post-surgical period. However, I see that despite being able to take adequate analgesics, patients' VAS scores are considerably different between the two groups, and between days 1 and 7 (Fig. 1).

I have three questions in this regard: (*5A*) The article reports higher analgesic doses used by the control group; were the higher NSAID doses used by the control group not sufficient to reduce their pains to about the pain levels felt by the laser group or lower? (*5B*) If not, why the sham group did not simply take even more NSAIDs to make sure they suffer the least? The dose of NSAID was a function of pain intensity. So why someone who was feeling a severer pain did not simply take as many capsules as needed to effectively alleviate his severer pain? It was quite possible and *also quite intuitive* for the sham group to remain on higher doses (say about 2.5 to 3 capsules a day) during the whole period, in order to ensure they suffer the least. Why did they not take more analgesics and instead suffered significantly more? (*5C*) Perhaps few patients in the sham group reached their maximum allowance (three capsules) in some of the days and could not take more analgesics. Still, most of the sham patients were on much lower doses than their allowance the whole week, despite their significantly greater pains, and despite the fact that they could simply double up their NSAID intake. Why do they counterintuitively choose to remain on much lower analgesic doses even though they had greater pains?

6. Yet another important question is that why the authors limited the maximum allowed daily dose of patients' analgesics to three capsules only? (*A*) What benefit did this limitation have? (*B*) Was it ***ethically justified*** to restrict the patients' control over their pain, while there was no benefit in such a control clinically or research-wise?
7. At one point, it was mentioned that pain was measured "till day 8". According to Table 1, it is apparently until day 7, while in Table 2, it is until day 8, but with day 6 missing (seven entries). Please clarify.
8. There was no mention of standardizing the time of scoring the pain VAS throughout the day. Pain might be felt more severe in the afternoon and milder in the morning [2]. So if the timing of pain measurement was not standardized among the patients or between the laser/sham sides of each patient, it might bias the results.
9. Also, estrogen levels might alter pain sensitivity [3]. So perhaps taking oral contraceptives should have been considered as an exclusion criterion. Perhaps, caution should have been used to ensure that the included women are across the same menstrual cycle phase (either among different women or between the two surgeries of the same woman).
10. When asked about their pain, did the patients report their pain levels felt immediately at the moment they were questioned? Or did they estimate an average of the pain they had felt during the last 24 h and reported that estimated average as the VAS score for that particular day? If an average was estimated, was it reliable?
11. Since the two surgeries on each patient were separated, was it possible for the systemic inflammatory response (caused by the surgery trauma) and stress of the first surgery to confound the outcomes of the second surgery? Pain perception might be affected by levels of physiological trauma and inflammation plus psychological stresses and the previous experience of pain, and a previous surgery can alter these components.
12. Did the patients undergo changes in diet or methods of oral hygiene control after the first surgery? If so, I think that should have been clarified in the article, and the confounding effect of such modifications (after the first surgery) on the outcomes of the second surgery should have been addressed. For example, a softer diet might affect the systemic health as well as plaque accumulation, and these might have affected the swelling and inflammation extents in the second surgery, which might in turn affect pain.
13. There were pre-surgical preparations (such as scaling, polishing, or plaque control) before the first surgery, but not before the second surgery. So I think the two control/experimental sides might not have been completely matched (as was expected in a split-mouth design).
14. Maybe a longer recovery duration might be needed to ensure that the patient's diet or oral hygiene control had returned back to normal for a sufficient time, before the second surgery. And before the second surgery, another round of plaque removal should have been performed.
15. There was no mention of any randomization of the first and second interventions over time. The order of interventions (implied from the order of their explanation in the text) seemed to be always laser first followed by sham. If the order of these interventions (to determine which one to come first) had been randomized, many

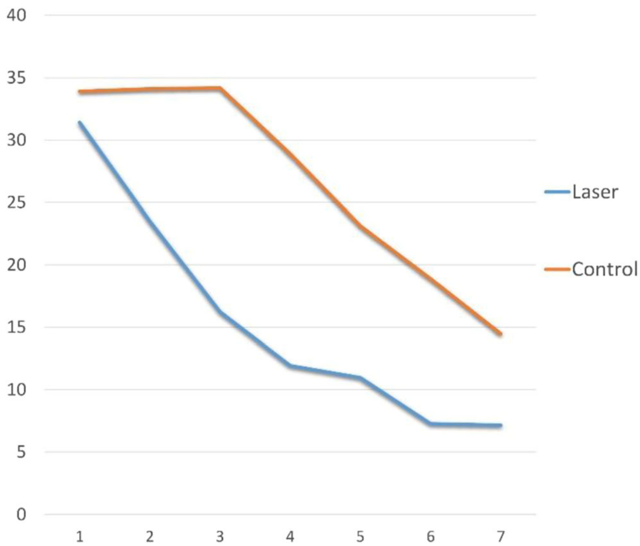

Fig. 1 VAS trends, drawn based on mean VAS values reported in Table 1 of Heidari et al. [1]

confounding effects might have been neutralized, because in half of patients, the laser treatment would be in the first session, while in the rest, it would be in the second session.

16. Antibiotics might not be necessary after periodontal surgeries (because of their important hazards together with the low incidence of infection after the surgery without antibiotics) [4–6]; moreover, some antibacterial agents might affect the levels of post-surgical pain [7]. Therefore, since antimicrobial agents (both antibiotics and chlorhexidine) might confound pain results, and since antibiotic prophylaxis after periodontal surgery might not be recommended [4–6], perhaps it was better to limit the use of antimicrobials to the minimum necessary dose of chlorhexidine only.

I should emphasize that this study was indeed a valuable and interesting research, with a large sample and laborious methodology, and controlling numerous factors. Understandably, almost all studies can have some limitations.

Source of funding The study was self-funded by the author.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Heidari M, Fekrazad R, Sobouti F, Moharrami M, Azizi S, Nokhbatolfoghahaei H, Khatami M (2018) Evaluating the effect of photobiomodulation with a 940-nm diode laser on post-operative pain in periodontal flap surgery. Lasers Med Sci 33:1639–1645
2. Aviram J, Pud D, Shochat T (2013) Pain sensitivity in healthy young men is modified by time-of-day. Sleep Med 14:e265
3. Hellström B, Anderberg UM (2003) Pain perception across the menstrual cycle phases in women with chronic pain. Percept Mot Skills 96(1):201–211
4. Oswal S, Ravindra S, Sinha A, Manjunath S (2014) Antibiotics in periodontal surgeries: a prospective randomised cross over clinical trial. J Indian Soc Periodontol 18(5):570–574. https://doi.org/10.4103/0972-124X.142443
5. Arab HR, Sargolzaie N, Moeintaghavi A, Ghanbari H, Abdollahi Z (2006) Antibiotics to prevent complications following periodontal surgery. Int J Pharmacol 2(2):205–208
6. Mohan RR, Doraswamy DC, Hussain AM, Gundannavar G, Subbaiah SK, Jayaprakash D (2014) Evaluation of the role of antibiotics in preventing postoperative complication after routine periodontal surgery: a comparative clinical study. J Indian Soc Periodontol 18(2):205–212. https://doi.org/10.4103/0972-124X.131327
7. Cho H, David MC, Lynham AJ, Hsu E (2018) Effectiveness of irrigation with chlorhexidine after removal of mandibular third molars: a randomised controlled trial. Br J Oral Maxillofac Surg 56(1):54–59. https://doi.org/10.1016/j.bjoms.2017.11.010