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OPEN PEER REVIEW

Effect of Low-Level Laser Therapy Combined with Therapeutic Ultrasound on Hand Pain and Function Following Carpal Tunnel Syndrome: A Randomized Controlled Trial

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

5 comments · 16 May 2021 – 7 Jun 2021

Referee 1 Reviewer

REJECT 16 May 2021

Dear AE,
This article examines the effects of two treatments (US and low-level laser therapy) and their combination on CTS. The writing of the article is very poor and needs to be completely rewritten by a native English speaker.
- Please specify whether the CTS was in the acute or chronic phase.
- What is stated in the findings section does not indicate that any of the three treatment groups had better outcomes than the others. On what basis do the researchers claim that combination therapy was more effective than the other two treatments?
- In the abstract section, 81 wrists are mentioned, while in the results section, 60 wrists are mentioned. - Please make these numbers consistent.
- In the introduction, it is mentioned that according to previous research, each treatment method alone is effective in treating CTS and neither is superior to the other. What is the need for combination therapy? Is there a gap in either treatment that the other treatment should fill? There does not seem to be a rational justification for offering combination therapy when each treatment alone can be effective in treating CTS.
- The section on treatment group assignment is very incomplete. In cases where both hands were involved, how was each hand assigned to a treatment? How was this allocation done in cases where one hand was involved? These data should be listed separately in the findings section.
- Indicate the type of devices and the manufacturer in the hand strength assessment section.
- Were the studied variables the same before the study in the three treatment groups? Refer to the statistical method used.
- The findings in Table 3 also show no difference between the three treatment groups, while the researchers conclude that combination therapy is more effective. Please provide the effect size if a clinical effect is present.
- In the tables, please report the mean changes as well.
- In the discussion section, it is better to point out the physiological mechanisms involved in combination therapy.
- Given the duration of CTS, which appears to have been in the chronic phase, what is the reason for using pulsed US?
Thanks.

Referee 2 Reviewer

MINOR REVISION 28 May 2021

Dear AE,
Comments for the authors:
- The text is very fluent, but the spelling mistakes should be checked (for example, “moth sensory and motor fibers”).
- For the sample size, please indicate the mean and SD values for both the patient and healthy groups from the previous study (20).
- Please mention the size of ERA in US treatment.
- In your study design, why didn't you have a control group (no treatment)? Please cite and explain it in the discussion.
“Among the limitations of the study, one could mention the small sample size, no follow-up, and

electromyographic not being recorded in the final sessions" None of these is a limitation. Please correct it.
" the combination of both modalities in each therapy session appears to have a better impact on treating these patients." Please correct this; your result was not significant. Please add MAY.
Thanks.

Referee 3 Reviewer

MAJOR REVISION 6 Jun 2021

Dear AE,
There are many typographical and grammatical errors. So, the manuscript needs to be edited throughout.
- A table should be added regarding the test-retest reliability of the hand dynamometer, with ICC and SEM measures.
- It is very important that there was no significant difference between groups in any of the main variables at baseline. So, these differences should be added to table 2.
- The subjects in the three groups were prescribed night splints. How did you determine that the changes in the variables were not related to the splints?
- In the discussion, the author(s) only compared their results with other research. There are no physiological explanations regarding the significant differences between the three groups in all variables.
Thanks.

Associate Editor

MAJOR REVISION 6 Jun 2021

Dear EIC
The reviewer(s) have recommended publication, but also suggest some major revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

Editor-in-Chief

MAJOR REVISION 7 Jun 2021

Dear Authors
According to the reviewers' and associate editor's comments, fundamental methodological and grammatical problems are present in your article, and it requires major revision. Please respond to the reviewers' comments and submit the required files.
Thanks.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear chief editor,

Thank you for reviewing our article entitled "**Effect of Low-level Laser Therapy Combined with Therapeutic Ultrasound on Hand Pain and Function Following Carpal Tunnel Syndrome: A Randomized Controlled Trial**" for publication in your journal.
We considered the reviewers' comments and revised the entire article. These insightful comments improved the scientific quality of our article greatly.
We provide a point-by-point response to the reviewers' comments. We hope that the changes made will be accepted and our article will be ready for publication in this journal.

Best regards
Corresponding Author

Response to Reviewer 1:

1- For sample size please indicate the mean and SD values for both the patient and healthy groups from the previous study.

- **The mean ± standard deviation of VAS in the ultrasound and laser groups was 4.9±1.46 and 2.6±1.07, respectively, which is indicated in the manuscript.**

2- Please mention size of ERA in US treatment.

- **The effective radiation area (ERA) of US was 5 cm^2 that is mentioned in the Method section.**

3- In your study design, why didn't you have a control group (no treatment)? Please cite and explain it in discussion.

- **Since the patients were referred to our physiotherapy center by a physician for physiotherapy, it was not possible to have a control group due to ethical considerations. In the Discussion section, explanations are provided about the lack of a control group**.

4- Among the limitations of the study, one could mention the small sample size, no follow-up, and electromyographic not being recorded in the final sessions" no one is limitation. Please correct it.

- **It was corrected.**

5- " the combination of both modalities in each therapy session appears to have a better impact on treating these patients." Please correct it your result was no significant please add MAY

- **It was corrected.**

Response to Reviewer 2:

1- The writing of the article is very poor and needs to be completely rewritten by a native English

- **The manuscript was grammatically and typographically revised.**

2- Please specify whether the CTS was in acute or chronic phase?

- **These were in the chronic phase, which is indicated in the manuscript**.

3- What is stated in the findings section does not indicate that there was a preference between the three treatment groups. On what basis do researchers claim that combination therapy has been more effective than the other two?

- **The mean changes in pain intensity, pinch grip, handgrip, symptom severity, and functional status were higher in the ultrasound and laser combination therapy group compared to the other two groups (laser therapy and ultrasound therapy), although no significant difference was observed between the groups**. **Since the therapeutic effects of the interventions may appear a few weeks after the end of the treatment, the lack of follow-up may explain the absence of a significant difference among the three groups. Thus, we conclude that the combination of these two treatment methods may be more effective in improving patients' symptoms and their hand function.**

4- In the abstract section, 81 wrists are mentioned, while in the results section, 60 wrists are mentioned. Please be the same.

- **It was corrected.**

5- In the introduction, it is mentioned that according to previous researches, each of the treatment methods alone is effective in treating CTS and has no precedence over each other. What is the need for combination therapy? Is there a gap in any treatment that another treatment should fill? There does not seem to be a rational justification for offering combination therapy when each treatment alone can be effective in treating CTS.

- **According to previous studies, both ultrasound and laser modalities have beneficial impacts on improving CTS symptoms through various mechanisms; thus, a combination of interventions (laser and ultrasound) may have a cumulative effect, producing an even more effective treatment regime, with superior and longer-lasting improvement.**

6- The section of assigning treatment groups is very imperfect. In cases where both hands were involved, how was each hand assigned to a treatment? How was this allocation done in cases where one hand was involved? This data should be listed separately in the findings section.

- **Patients with bilateral CTS had both hands placed in the same group, and the intervention was the same for both hands. The evaluations were performed separately for the two hands**.

7- Indicate the type of devices and the manufacturer in the hand strength assessment section

- **Pinch grip and handgrip strengths were measured using a dynamometer (Model SH-5003, SAEHAN Company, South Korea).**

8- Were the studied variables the same before the study in the three treatment groups? Refer to the statistical method used.

- **There were no significant differences in the dependent variables among groups before the therapy sessions, which is presented in Table 2 (P>0.05).**

9- The findings in Table 3 also show no difference between the three treatment groups, while the researchers conclude that combination therapy is more effective. Please provide effect size if clinical effect is present.

- **Although the mean changes in pain intensity, pinch grip, handgrip, symptom severity, and functional status were higher in the ultrasound and laser combination therapy group compared to the other two groups (laser therapy and ultrasound therapy), no significant difference was observed between the groups (P>0.05). We conclude that the**

combination of these two treatment methods may be more effective in improving patients' symptoms and hand function.

10- In the tables, please report the mean changes as well.

- **The mean changes of variables are presented in Table 3**

11- In the discussion section, it is better to point out what mechanisms the combination therapy physiologically involves.

- **The exact mechanism of the beneficial impacts of a combination of ultrasound and low-level laser in treating CTS is yet to be known. Through two distinct mechanisms, ultrasound and laser induce beneficial effects on pain relief and improvement of CTS symptoms. Ultrasound can stimulate tissue regeneration and anti-inflammatory effects by reducing the pressure inside the carpal tunnel, decreasing the inflammation around the nerve, and accelerating the damaged tissue's repair. Low-level laser relieves pain and reduces inflammation locally by stimulating microcirculation, blocking pain enzymes, and activating endorphin enzymes. It seems that the simultaneous use of both modalities on the carpal tunnel can activate the mechanisms related to each of these two modalities in this area. Therefore, a combination of laser and ultrasound may have a cumulative effect, producing an even more effective treatment regime and superior and longer improvement. However, more studies are required on the mechanisms of ultrasound and laser combination.**

12- Given the duration of the CTS, which appears to have been in the chronic phase of CTS, what is the reason for using the pulse US?

- **The results of previous studies (8, 18, 21) demonstrated that pulse US has a beneficial effect on treating CTS. Pulsed-mode US therapy effectively enhanced peripheral nerve regeneration in an animal study, possibly through the mechanisms of local blood vessel dilatation, nerve sprouting stimulation, Schwann cell activation, and chemotactic stimulator release [9]. However, the present study had the advantage of the selection of pulsed mode with its positive effects on tissue regeneration.**

Response to Reviewer 3:

1- There are many typography and grammatical errors. So, the manuscript needs to be edited totally.

- **The manuscript was revised grammatically and typographically.**

2- A table should be added regarding the test-retest reliability of hand Dynamometer with ICC and SEM measures.

- **The dynamometer reproducibility test and the result of intraclass correlation coefficient (ICC) using Munro table (very low: 0.00-0.25; low: 0.26-2.49; medium: 0.50-0.69; good: 0.70-0.89; and excellent: 0.90-100) showed excellent reproducibility. Studies have indicated that the validity and reliability of the SAEHAN dynamometer are high, and it is considered to be the gold standard for assessing handgrip strength (21).**

3- It is very important that there were no significant difference between groups in all main variables at the baseline. So, in the table 2 these difference should be added.

- **There were no significant differences in the dependent variables among groups before the therapy sessions, which is presented in Table 2 (P>0.05).**

4- The subjects in three groups were prescribed to use night splint. How did you find out that the changes in the variables are not related to splints?

- **We used a wrist orthosis with treatment interventions (US, laser, and a combination of US and laser) because it would have been unethical to withhold wrist orthosis. Therefore, the treatment effects might partially originate from wrist orthoses. Nevertheless, given that the splint was used in all three groups, its positive effects can be assumed to be similar in all the three groups**.

5- In the discussion the author(s) only compared their results with other researches. There is no physiological explanations regarding the no significant differences between the three groups in all variables.

- **In this study, all the variables were evaluated immediately after the last session. As the therapeutic effects of the interventions performed may appear a few weeks after the end of the treatment, it seems that the lack of follow-up may explain the absence of significant differences among the three groups. In addition, a lack of significant results among groups may be due to the small sample size; subsequent studies are recommended to recruit a larger sample.**

2 Revision 1

4 comments · 20 Jul 2021 – 16 Aug 2021

Referee 2 Reviewer

ACCEPT 20 Jul 2021

Dear AE,
The study has been reviewed carefully. Based on the author's comments and revisions, this manuscript is accepted.
Thanks

Referee 3 Reviewer

ACCEPT 14 Aug 2021

Dear AE,
The author(s) replied to all the questions. The manuscript can be published.
Thanks.

Associate Editor

ACCEPT 15 Aug 2021

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

Editor-in-Chief

ACCEPT 16 Aug 2021

Dear Authors
We are pleased to inform you that your article is accepted for publication in the MEJRHS. We hope to receive other suitable articles from your group.
Thanks.