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Effectiveness of Low-Level Laser Therapy compared to Ultrasound in Patients With Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis

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Abstract

Introduction: Carpal tunnel syndrome (CTS) is the most common type of peripheral entrapment neuropathy that occurs in the wrist area in a space called the carpal tunnel. Low-level laser therapy (LLLT) and ultrasound are among the most common methods of physical modalities for treating CTS; the effectiveness of these 2 methods and the superiority of one over the other are not agreed among experts.

Methods: In the present systematic review and meta-analysis study, the most important databases including PubMed, Cochrane Library, Scopus, Centre for Reviews and Dissemination, Science Direct, Trip medical database and Google Scholar were searched using appropriate keywords and specific strategies without time limitation to collect data. The collected data was analyzed using the meta-analytic method and the random-effects model. The heterogeneity among studies was examined using I^2. The data were analyzed using Review Manager Software.

Results: From among 108 related studies, 49 cases were entered for the first stage. After the final examination, 6 studies were selected for meta-analysis. The total number of patients in these 6 studies was 403; 204 subjects were in the LLLT group and 199 subjects were in the ultrasound group. The results of the meta-analyses showed that there was no significant difference between these 2 therapeutic methods in terms of pain relief, symptom severity scale (SSS), functional status scale (FSS), motor latency, sensory latency, hand grip strength, and motor amplitude.

Conclusion: Based on the meta-analyses, there was no significant difference between the 2 LLLT and ultrasound methods; in other words, they had similar effectiveness in improving the condition of patients with CTS. However, the authors believe that arriving at conclusions in this area requires high-quality and large size studies.

Keywords: Carpal tunnel syndrome; Low-level laser therapy (LLLT); Ultrasound; Meta-analysis.

Introduction

Carpal tunnel syndrome (CTS) is the most common type of peripheral entrapment syndrome that occurs in the wrist area in a space called the carpal tunnel.[1] This syndrome is a hand debilitating disease which, if not treated, causes median nerve damage and as a result, loss of hand function.[2]

The carpal tunnel consists of wrist bones and transverse ligament (flexor retinaculum) in anterior part of the wrist and the median nerve passes through this space with 9 tendons.[3] Due to its specific position in the tunnel, the median nerve is highly prone to compression and in some cases, this syndrome occurs due to repetitive wrist activities.[4] In repeated flexion and extension of the wrist, the pressure in tunnel increases and the nerve is compressed further.[5] The pressure inside this space varies from 18 to 47 mm Hg in different positions in the wrist. The studies show that the incidence among women is 4 times higher than men; it seems that working factors play an effective role in developing this syndrome.[6]

The risk factors associated with CTS include repetitive activities that require the wrists to bend and straighten, hysterectomy without oophorectomy, 6 to 12 months after the last period in postmenopausal women, pregnancy, and

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shorter height and higher weight.[7,8] Most patients with CTS complain of weakness, paresthesia, and numbness of fingers in median nerve territory. Many patients also suffer from wrist pain at night or after much work with their hands or fingers. In the advanced cases of the disease, the weakness of thumb and index fingers along with atrophy of relevant muscles results in the inability to grip and falling of objects from hand.[9]

There are different methods to treat CTS, including medication,[10] splint, exercises,[11] surgery,[12] low-level laser therapy (LLLT),[13-15] Bioptron,[16] and ultrasound.[17] Among various therapies, the LLLT and ultrasound methods may have potential effects on inducing biophysical effects within tissues.[18,19] The experiments on nerve regeneration and neurotransmission, which are affected by LLLT[20,21] and ultrasound[22,23] stimulatory effect, suggest that these treatments may facilitate the recovery process in the compressed nerve. The anti-inflammatory mechanisms, improvement of the vascular supply, and production of myelin in the median nerve, which may lead to nerve reconstruction, reflect the possible effects of LLLT on CTS treatment.[24]

Since LLLT and ultrasound are the most common and the most effective physical medicine modalities for this disease and there is no comprehensive, up-to-date, and systematic study on the superiority of one over the other, this study aims to investigate the effectiveness of LLLT in comparison with ultrasound in patients with CTS, the result of which can be used as a tool for evidence-based policy-making and decision-making.

Methods

This study used the methodology of the Cochrane Institute for carrying out the systematic review of interventions in 6 stages.[25]

In the first stage, the following clinical question was designed based on PICOs (Population, Intervention, Comparator, Outcome studies) formulation (Box 1).

In the second stage, the most important electronic medical resources (PubMed, Cochrane Library, Scopus, Centre for Reviews and Dissemination), without time limitation until August 2019, based on search strategy specific to each database (Table S1, Supplementary file 1) and other websites (Science Direct, Trip Medical Database, Google Scholar) were searched and organized in EndNote software.

In the third stage, after the removal of repetitive articles, 2 researchers independently selected the studies based on the inclusion and exclusion criteria and the research question. The review and selection of articles were conducted based on the PRISMA diagram.[26] In the selection of studies, their title, their abstract, and their full text were investigated and any disagreement at this stage was resolved by consensus and considering the third researcher's opinion. At the end of this stage, the references of the individual articles were searched manually to ensure that the relevant articles were not lost.

Box 1. Components of the Clinical Question

- Population: Patients with carpal tunnel syndrome;
- Intervention: Low-level laser therapy;
- Comparator: Ultrasound;
- Outcome: Pain Relief, Symptom Severity Score, Functional Status Scale, Visual Analogue Score, Grip Strength, Motor Latency, Sensory Latency, Motor Amplitude;
- Type of studies: Clinical Trials relevant to our PICO.

In the fourth stage, 2 individuals independently evaluated the quality of articles based on Jadad quality assessment criteria[27] and 5 indices: (1) Is the study randomized? (2) Is the randomization procedure appropriate and reported in the study? (3) Is the study double-blind? (4) Is the double-blind method appropriate and reported in the study? (5) Are the reasons for patient withdrawals and dropouts described for each treatment group? Any disagreements were resolved by consensus and considering the third researcher's opinion.

In the fifth stage, a special form in Excel 2013 was designed to extract the data from the selected articles. This form consists of 3 parts: (1) General information of articles (such as corresponding author, publication year, country, inclusion and exclusion criteria, age of patients, number of patients, etc); (2) Statistical data related to each outcome (sample size in each group, mean and standard deviation of each outcome in each group, follow-up duration); and (3) Features of treatment (e.g. the wavelength applied in LLLT, the frequency used in ultrasound, the number of treatment sessions per group, etc).

In the sixth stage, the data were analyzed using the meta-analysis method in Review Manager software. This study used a standardized mean difference based on the reverse variance and random statistical model in a 95% confidence interval to determine the effect size. The heterogeneity was determined based on I^2 statistic at the 0.05 confidence level; if this statistic is more than 40% and the *P* value is less than 0.05, there is a significant heterogeneity whose reasons should be investigated.

Results

A total of 129 articles were found in a search of medical electronic databases as well as other information sources. After the removal of 21 repetitive articles, 108 articles remained. Considering the title and abstract, 59 articles were recognized as unrelated and removed. The full text of 18 remaining articles was extracted and reviewed. Finally, 6 articles published between 2004 and 2019 were selected for analysis (Figure 1).

The total number of patients in these 6 studies was 403; 204 subjects were in the LLLT group and 199 subjects were in the ultrasound group. The mean age of patients in the LLLT group was at least 35.1 and at most 52.2 and in the ultrasound group was at least 36.08 and at most 51.4.

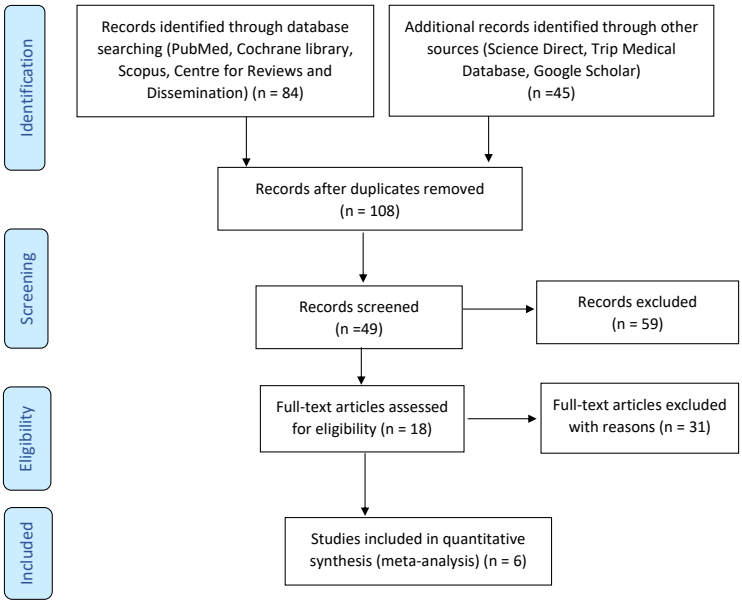

Figure 1. The Process of Search and Selection of Studies (PRISMA Diagram).

The duration of follow-up effects in these articles varied between 2 weeks to 12 months. The characteristics of the studied articles are presented in Tables 1-3.

The quality of studies was evaluated based on Jadad scoring scale.[27] Based on consensus among 3 evaluators, 1 study scored 4, 4 studies scored 3, and 1 study scored 2 (Table S2, Supplementary file 1).

Pain Relief

In general, 6 articles examined the outcome of pain relief based on the visual analogue scale (VAS) on a 10 cm linear range. The examination periods in Bartkowiak et al,[33] Bakhtiary & Rashidy-Pour,[28] Dincer et al[29], Saeed et al[30], Ahmed et al[32] and Tikiz et al[31] studies were 2-3 weeks, 1 month, 1 & 3 months, 1 month, 6 weeks, and 3 & 6 and

Table 1. Characteristics of the Studied Articles

First Author	Year	Country	Inclusion Criteria	No. of Patients or Wrists		Mean Age		Follow-up Time
				LLLT	US	LLLT	US	
Bakhtiary[28]	2004	Iran	Positive Phalen's test, positive Tinnel's test, and standard electrophysiological criteria including prolongation of nerve conduction velocity (i.e., motor latency > 4 ms or sensory latency > 3.5 ms)	45 wrists	45 wrists	48 (13.4)	45 (17.1)	4 weeks
Dincer[29]	2009	Turkey	CTS diagnosis was made with clinical examination and electroneuromyography (ENMG), having mild, moderate, or advanced CTS according to the American Association of Electrodiagnostic Medicine guidelines	36 wrists	30 wrists	52.2 (9.1)	49.7(9.5)	1 & 3 months
Saeed[30]	2012	Pakistan	Unilateral idiopathic CTS, with symptoms were more than 4 months of duration, patients with no other compressive neuropathy and generalized neuropathy on electrodiagnosis.	50 patients	50 patients	35.1 (6.2)	36.08 (5.9)	4 weeks
Tikiz[31]	2013	Turkey	Patients with paresthesia, pain and / or vasomotor symptoms at the site of the median nerve distribution in their history, those with night complaints, longer than 6 weeks of symptom duration, and at least one of the Tinel, Phalen and Reverse Phalen tests in their physical examination were included in the study	13 patients	14 patients	46.6 (8.6)	51.4 (6.3)	3, 6 and 12 months
Ahmed[32]	2017	Egypt	Mild to moderate CTS in patients with diabetic peripheral neuropathy (DPN) T2DM	25 patients	25 patients	38.08 (1.11)	39.56 (1.49)	6 weeks
Bartkowiak[33]	2019	Poland	Diagnosis of the mild or moderate stage of CTS (according to criteria by Whitney and McDonnell) by an orthopedist or neurologist, symptom duration for more than 3 months, and general good health.	35 patients	35 patients	47.4 (11.1)	46.9 (10.8)	2-3 weeks

Table 2. Characteristics of Treatment With LLLT

Study	Wavelength	Intensity	Energy	Average Power	Time of Exposure	Sessions of Therapies	Total of Therapies
Bakhtiary[28]	830 nm	9 J	1.8 J/point, 5 points over the wrist	N.R	N.R	Once a day, 5 times a week for 3 weeks	15
Dincer[29]	904 nm	N.R	0.072 J/point, N.R	2.4 mW	30 s at each point	Once a day, 5 times a week, for 2 weeks	10
Saeed[30]	830 nm	9 J	1.8 J/point, N.R	N.R	N.R	Once a day, 5 times a week for 4 weeks	20
Tikiz[31]	830 nm	N.R	1.5 J/point, 5 points over the wrist	30 mW	5 min (1 min per point)	5-week period of 5 days per week	25
Ahmed[32]	904 nm	4.8 J	1.2 J/point, 4 points over the wrist	20 mW	4 min (1 min per point)	3 sessions weekly for 6 weeks	18
Bartkowiak[33]	830 nm	9 J	N.R, 5 points over the wrist	100 mW	10 min (2 min per point)	2 weeks (5 session times per week)	10

NR: Not Report.

Table 3. Characteristics of Treatment With Ultrasound

Study	Frequency	Intensity (Power)	Transducer Area	Mode Type	Time of Application	Sessions of Therapies	Total of Therapies
Bakhtiary[28]	1 MHz	1.0 W/cm^2	5 cm^2	Pulsed mode duty cycle of 1:4	15 min per session	Once a day, 5 times a week for 3 weeks	15
Dincer[29]	3 MHz	1.0 W/cm2	5 cm^2	Continuous mode	3 min per session	Once a day, 5 times a week, for 2 weeks	10
Saeed[30]	1 MHz	1.0 W/cm^2	N.R	N.R	N.R	Once a day, 5 times a week for 4 weeks	20
Tikiz[31]	3 MHz	1.0 W/cm2	1.4 cm2	Pulsed mode duty cycle of 1:4	10 min per session	5-week period of 5 days per week	25
Ahmed[32]	1 MHz	1.0 W/cm^2	N.R	Pulsed mode duty cycle of 1:4	15 min per session	3 sessions weekly for 6 weeks	18
Bartkowiak[33]	1 MHz	1.0 W/cm^2	5 cm^2	Pulsed mode duty cycle of 1:4	6 min over the area of the carpal tunnel	2 weeks (5 session times per week)	10

NR: Not Report.

12 months, respectively. Figure 2 shows the charts of this outcome at follow-up times of 2-4 weeks, 6 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that although the patients treated with ultrasound had a better VAS score, this difference was not statistically significant (standard mean difference [SMD] = 0.65; 95% CI: -0.1 to 1.41; $P = 0.09$). The result of the heterogeneity test showed that there was a significant difference in heterogeneity ($I^2 = 94\%$; $P \leq 0.00001$).

Symptom Severity Scale

In general, 4 studies examined the outcome of symptom severity scale (SSS) based on Boston questionnaire. The examination periods in Bartkowiak et al,[33] Dincer et al,[29] Saeed et al,[30] and Tikiz et al[31] studies were 2-3 weeks, 1 & 3 months, 1 month, and 3 & 6 and 12 months, respectively. Figure 3 shows the charts of this outcome at follow-up times of 2-4 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD = 0.24; 95% CI: -0.6 to 1.08; $P = 0.57$). The result of the heterogeneity test showed that there was a significant difference in heterogeneity ($I^2 = 93\%$; $P \leq 0.00001$).

Functional Status Scale

In general, 4 articles investigated functional status scale

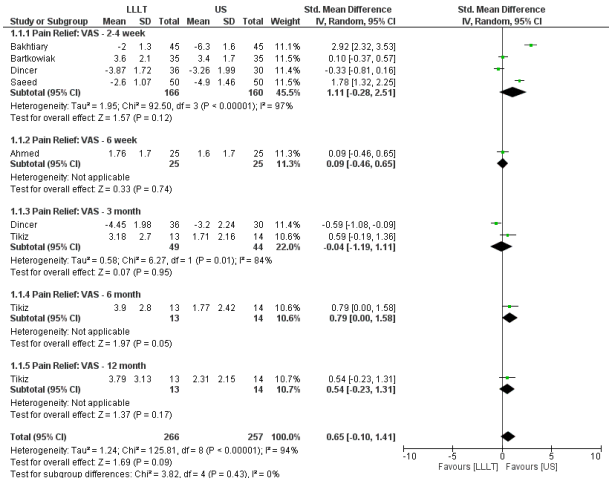

Figure 2. Comparison of Pain Relief Between the LLLT and US Treated Groups.

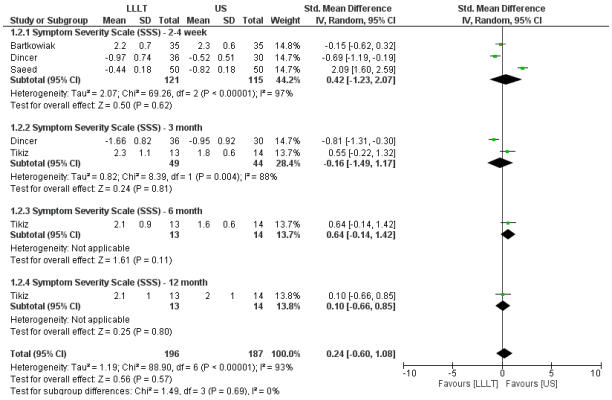

Figure 3. Comparison of SSS Between the LLLT and US Treated Groups.

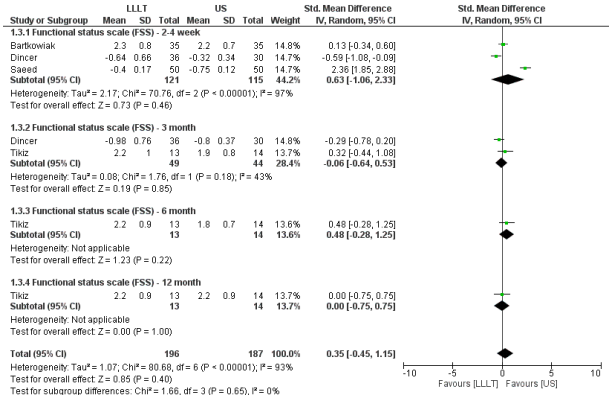

Figure 4. Comparison of FSS Between the LLLT and US Treated Groups

(FSS) outcomes based on Boston questionnaire. The examination periods in Bartkowiak et al,[33] Dincer et al,[29] Saeed et al,[30] and Tikiz et al[31] studies were 2-3 weeks, 1 & 3 months, 1 month, and 3 & 6 and 12 months, respectively. Figure 4 shows the charts of this outcome at follow-up times of 2-4 weeks, 3 months, 6 months, and 12 months. The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD = 0.35; 95% CI: -0.45 to 1.15; P = 0.4). The result of the heterogeneity test showed that there was a significant difference in heterogeneity (I^2 = 93%; $P \leq 0.00001$).

Motor Latency

In general, 5 studies examined motor latency. The examination period in Bakhtiary & Rashidy-Pour,[28] Dincer et al[29], Saeed et al,[30] Ahmed et al,[32] and Tikiz et al[31] studies were 1 month, 1 & 3 months, 1 month, 6 weeks, and 3 & 6 and 12 months, respectively. Figure 5 shows the charts of this outcome at follow-up times of 1 month, 6 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD = 0.59; 95% CI: -0.39 to 1.58; P = 0.24). The result of the heterogeneity test showed that there was a significant difference in heterogeneity (I^2 = 95%; $P \leq 0.00001$).

Sensory Latency

In general, 5 studies examined the sensory latency outcomes. The examination periods in Bakhtiary & Rashidy-Pour,[28] Dincer et al,[29] Saeed et al,[30] Ahmed et al,[32] and Tikiz et al[31] studies were 1 month, 1 & 3 months, 1 month, 6 weeks, and 3 & 6 and 12 months. Figure 6 shows the charts of this outcome at follow-up times of 1 month, 6 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD =

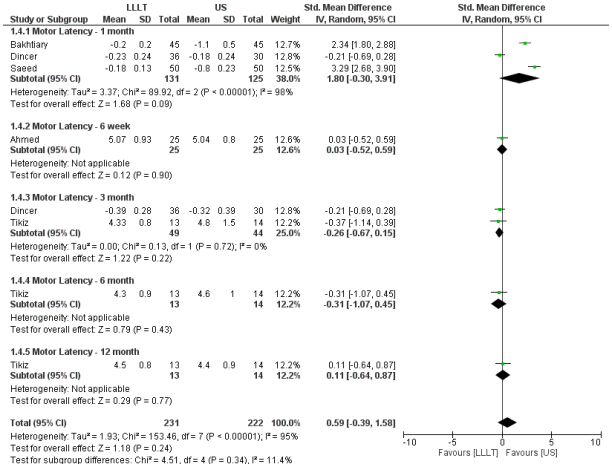

Figure 5. Comparison of Motor Latency between the LLLT and US Treated Groups.

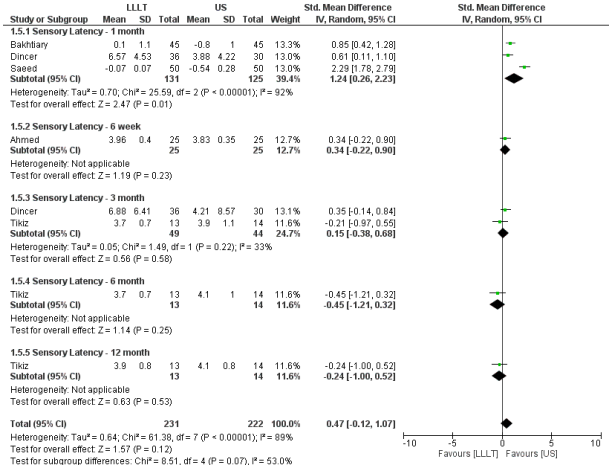

Figure 6. Comparison of Sensory Latency Between the LLLT and US Treated Groups.

0.47; 95% CI: -0.12 to 1.07; P = 0.12). The result of the heterogeneity test showed that there was a significant difference in heterogeneity (I^2 = 89%; $P \leq 0.00001$).

Hand Grip Strength

In general, 4 studies examined hand grip strength. The examination periods in Bartkowiak et al,[33] Bakhtiary & Rashidy-Pour,[28] Ahmed et al,[32] and Tikiz et al[31] studies were 2-3 weeks, 1 month, 6 weeks, 3 & 6 and 12 months. Figure 7 shows the charts of this outcome at follow-up times of 2-4 weeks, 6 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD = -0.17; 95% CI: -0.61 to 0.31; P = 0.27). The result of the heterogeneity test showed that there was a significant difference in heterogeneity (I^2 = 69%; P = 0.006).

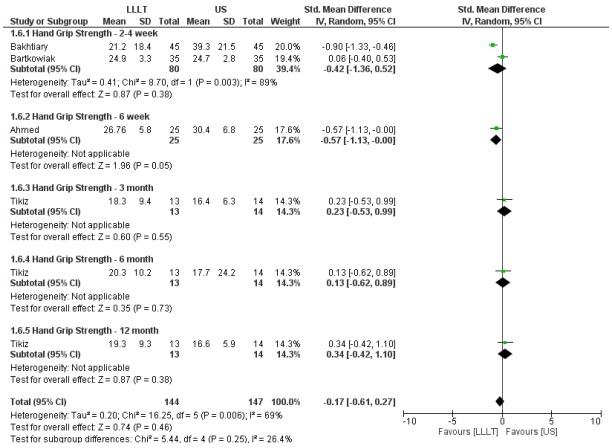

Figure 7. Comparison of Hand Grip Strength Between the LLLT and US Treated Groups.

Motor Amplitude

In general, 3 studies examined motor amplitude. The examination periods in Bakhtiary & Rashidy-Pour,[28] Ahmed et al,[32] and Tikiz et al[31] studies were 1 month, 6 weeks, and 3 & 6 and 12 months, respectively. Figure 8 shows the charts of this outcome at follow-up times of 1 month, 6 weeks, 3 months, 6 months, and 12 months.

The overall result of meta-analyzing this outcome showed that there was no statistically significant difference between these 2 groups in terms of this outcome (SMD = -0.34; 95% CI: -0.8 to 0.11; P = 0.14). The result of the heterogeneity test showed that there was a significant difference in heterogeneity (I^2 = 55%; P = 0.06).

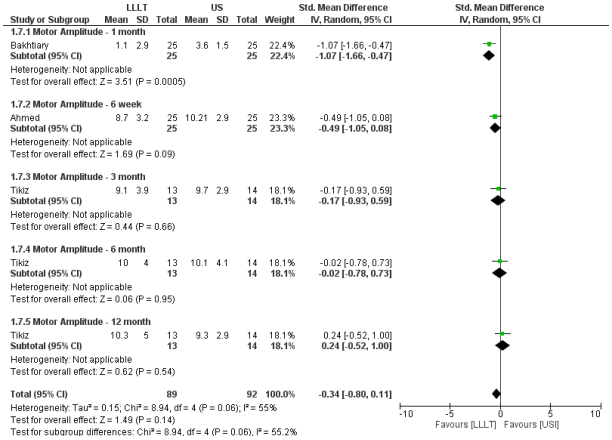

Figure 8. Comparison of Motor Amplitude Between the LLLT and US Treated Groups.

Discussion

Using systematic review and meta-analysis, this study evaluated the effectiveness of LLLT in comparison with ultrasound in patients with CTS based on 7 outcomes: (1) pain relief, 2) SSS, (3) FSS, 94) hand grip strength, (5) sensory latency, (6) motor latency, and (7) motor amplitude. This study analyzed 6 randomized clinical trials which examined 403 samples during a follow-up period from 2 weeks to 12 months. The quality assessment of studies was conducted based on Jadad criteria[27]; it was shown that only one article had acceptable quality and other articles generally had poor quality.

Four articles compared LLLT and ultrasound methods without any quantitative treatment. Dincer et al[29] used splint and Bartkowiak et al[33] used gliding exercises along with LLLT and ultrasound. All studies examined the outcomes in the short term in less than 3 months except Tikiz et al[31] who followed up the outcomes for up to 12 months.

Ahmed et al[32] studied diabetic patients with type 2 diabetes mellitus (T2DM) peripheral neuropathy with mild to moderate CTS. Dincer et al[29] studied the patients who had mild, moderate or advanced CTS based on the American Association of Electrodiagnostic Medicine (AAEM) guideline. Bartkowiak et al[33] studied the patients with mild to moderate CTS based on Whitney and McDonnell criteria. Three other studies investigated the patients with idiopathic CTS who were diagnosed by similar criteria.

The wavelength of laser therapy in the studies by Dincer et al[29] and Ahmed et al[32] was 904 nm and in other studies, it was 830 nm. The duration of radiation exposure varied from 30 seconds in Dincer et al study up to 2 minutes in Bartkowiak et al study. The severity was not reported in the studies by Tikiz et al[31] and Dincer et al[29]; it was 4.8 J in Ahmed et al[32] study and 9 J in other studies. The total number of treatment sessions in the studies by Dincer et al[29] and Bartkowiak et al[33] was 10, in Bakhtiary and Rashidy-Pour[28] study was 15, in Ahmed et al[32] study was 18, in Saeed et al study was 20, and in Tikiz et al[31] study was 25. The frequency of ultrasound was 3 kHz in the studies by Dincer et al[29] and Tikiz et al[31] and it was 1 kHz in other studies. The duration of exposure to radiation varied from 3 minutes in Dincer et al[29] study to 24 minutes in the studies by Ahmed et al[32] and Bakhtiary & Rashidy-Pour.[28] The intensity and power used in all studies was 1.0 W/cm^2. The total number of treatment

sessions in the studies conducted by Dincer et al,[29] Bartkowiak et al,[33] Bakhtiary & Rashidy-Pour,[28] Ahmed et al,[32] Saeed et al,[30] and Tikiz et al[31] were 10, 10, 15, 18, 20, and 25 respectively. Dincer et al[29] used a continuous mode, Saeed et al did not report it, and other studies used a pulsed mode duty cycle of 1: 4.

The analysis of the studied articles showed that there was no significant difference or significant clinical benefit in pain relief (SMD = 0.65; 95% CI: -0.1 to 1.41; $P = 0.09$), SSS (SMD = 0.24; 95% CI: -0.6 to 1.08; $P = 0.57$), FSS (SMD = 0.35; 95% CI: -0.45 to 1.15; $P = 0.4$), motor latency (SMD = 0.59; 95% CI: -0.39 to 1.58; $P = 0.24$), sensory latency (SMD = 0.47; 95% CI: -0.12 to 1.07; $P = 0.12$), hand grip strength (SMD = -0.17; 95% CI: -0.61 to 0.31; $P = 0.27$), and motor amplitude (SMD = -0.34; 95% CI: -0.8 to 0.11; $P = 0.14$) in treating CTS with ultrasound or LLLT. In all meta-analyses, the result of the heterogeneity test was significant and the I^2 statistic was calculated to be between 55% and 95%.

Studying the effectiveness of LLLT in comparison with non-surgical therapeutic methods such as ultrasound, Rankin et al[34] analyzed 3 articles (Saeed, Tikiz, and Bakhtiary). In this study, the meta-analysis of SSS and FSS outcomes based on the articles authored by Tikiz et al[31] and Saeed et al[30] showed that ultrasound therapy was superior without any heterogeneity. There was no significant difference in grip strength, but the results of pain relief, sensory latency, and motor latency were reported in favor of ultrasound; heterogeneity with I^2 statistic of 65% to 89% was significant in these analyses. The present study investigated 6 articles; 2 cases used other methods along with LLLT and ultrasound interventions. Dincer et al[29] used splint and Bartkowiak et al[33] used gliding exercises along with LLLT and ultrasound. In this study, it was assumed that splint or gliding exercises, if useful, may increase the effectiveness of both methods similarly. For this reason, it was determined that these 2 studies should be analyzed along with other articles. Additionally, in another study,[32] the treated patients were different from the patients of other articles. In this study, the population consisted of peripheral neuropathy diabetic patients (T2DM) with mild to moderate CTS. Due to diabetes disease caused by peripheral neuropathy (T2DM), it seems that the effectiveness of LLLT and ultrasound methods in this study is different from the other studies.

In the meta-analysis of all outcomes, the I^2 statistic, which is the criterion for the presence of heterogeneity, was calculated to be between 55% and 95%; this indicates a high heterogeneity level. The reasons for heterogeneity and analysis limitations in this study are as follows.

The treated population is not included by similar criteria. It seems that the stage, severity, cause of disease, and presence of disease associated with CTS may affect the effectiveness of treatment. Another factor may be found in therapeutic procedures (including frequency or intensity used in ultrasound or the wavelength and energy used in laser radiation). In addition, the duration of exposure, the number of wrist exposure points, and the number of treatment sessions are also the variables which are investigated in the analyzed articles and it seems that they may cause heterogeneity and impact on the effectiveness of treatment and outcomes. In Tikiz et al[31] study, the sample size in the laser group was 13 and in the ultrasound group was 14; this low sample size caused bias in its results. In addition, the quality evaluation indicated that its quality was low.

Conclusion

Based on meta-analyses, there was no significant difference between LLLT and ultrasound methods; in other words, the effectiveness of both methods in treating patients with CTS was similar and none had superiority over the other. However, the authors argued that considering the limitations mentioned above and because of the low quality of evidence, arriving at a proper conclusion in this area requires high quality and large size studies.

Ethical Considerations

The study was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences and conducted in accordance with the ethical guidelines of the Declaration of Helsinki (IR.SBMU.RETECH.REC.1398.177).

Conflict of Interests

The authors declare no conflict of interest.

Supplementary Materials

Supplementary file 1 contains Tables S1-S2.

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