

Comparative effectiveness of low-level laser therapy and transcutaneous electric nerve stimulation in the treatment of pain caused by temporomandibular joint disorders: a systematic review and network meta-analysis

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Abstract

Background: The comparative effectiveness of low-level laser therapy (LLLT) and transcutaneous electric nerve stimulation (TENS) in the treatment of pain caused by temporomandibular joint disorders (TMD) has not been evaluated.

Methods: PubMed, Cochrane Library and Embase were searched from their inception until 27 October 2019. Randomized controlled trials (RCTs) that compared the effects of LLLT or TENS or placebo group for TMD patients' pain reduction were included. The reviewers assessed the risk of bias of individual studies with the Cochrane risk of bias tool, excluding RCTs with a high risk of bias in any domain. Then the reviewers did network meta-analysis and assessed the quality of evidence contributing to network estimate using the GRADE framework.

Results: 20 RCTs with 758 patients with TMD were included. In the pair-wise meta-analysis, LLLT and TENS showed a significant pain reduction in the visual analogue scale (VAS) compared with placebo immediately after treatment [mean difference (MD)=1.99, 95% confidence interval (CI):(1.07,2.92); MD=2.16, 95%CI:(0.27,4.04), respectively]. As for pain reduction one month after treatment, LLLT performed better and there was no statistically significant difference for TENS as compared with placebo.

Conclusion: The results of this meta-analysis showed the short-term efficacy of LLLT is more positive than TENS in the treatment of pain caused by temporomandibular joint disorders.

Background

Temporomandibular joint disorders (TMD) is a collective term for clinical problems in masticatory muscles, temporomandibular joint (TMJ), and surrounding structures, which present as pain, joint and muscle tenderness, joint noises and limited or asymmetrical jaw movement [1–3]. Pain often occurs at any stage of TMD and is a significant component of the symptoms that prompt patients to seek treatment [4]. TMD pain usually results from the masticatory muscles, the TMJ and related structures or a combination of these [5]. However, the aetiology of most of TMD is still unclear [6–7]. Conservative therapies have been used as predominant methods for curing this condition, including supportive patient education, occlusal splint, medication and physical therapy [8]. There has been increasing attention on physical therapy as the American Academy of Craniomandibular Diseases treated physical therapy as the main treatment modality for TMD management [9]. Among various physical therapy interventions, acupuncture, exercises, massages, thermal therapy, transcutaneous electric nerve stimulation (TENS), ultrasound, and low-level laser therapy (LLLT) have been employed [10].

LLLT represents analgesic effects, anti-inflammatory and stimulative effects, which is a potential noninvasive treatment for TMJ pain [11]. Its exact mechanism of pain control is unknown. Reports suggested that this might occur because of increased release of endogenous negative ions, improved local microcirculation, or increased lymph flow, thereby reducing edema, increasing ATP production, and

decreasing the permeability of nerve cell membranes [12, 13]. TENS has also widely applied in the clinic given its analgesic and muscle relaxing effect, with positive results [10, 14]. The study reported that TENS promoted muscle relaxation and reduced pain perception through electromyographic and electrognathographic analysis [10]. Although neurophysiological mechanisms underlying TENS' induction of anti-pain sensitivity are not understood, it is showed that TENS activates opioid receptors at supraspinal sites [15].

Previously, several systematic reviews (SR) and network meta-analysis (NMA) studies researched the effectiveness of LLLT for pain relief in patients with TMD [16–27]. Meanwhile, De Giorgi.et al. and Ferreira.et al. [15, 28] proved that the therapeutic effects of TENS are superior to those of the placebo. In recent years, several RCTs compared LLLT with TENS for treating patients suffering from TMD [10, 12, 14, 29]. But there were only limited data comparing their relative efficacy with each other, and the statistical power was insufficient. Until now, no SRs on LLLT and TENS for TMD treatment have been reported. Thus, although the two treatment options appear to be superior over placebo in alleviating pain, more effective treatment is still currently unknown. Therefore, reviewers conducted this systematic review and network meta-analysis to compare relative efficacy between two therapies in the treatment of pain caused by temporomandibular joint disorders.

Methods

Inclusion and exclusion criteria

Reviewers included RCTs comparing LLLT or TENS or placebo group in the treatment of TMD, no matter the type of laser and the amount of energy density or power. Studies evaluated at least the two modalities, including sham therapy. Reviewers excluded RCTs recruiting participants with trauma or systematic diseases or pregnancy. Reviewers chose pain intensity reduction immediately after treatment as the primary outcome, and the secondary outcome included the change of pain intensity between the baseline and the end of one-month follow-up. So studies included RCTs that contained at least one subjective pain evaluation that was the same as or similar to the 0–10 cm visual analogue scale (VAS). If there were no explicit reports, reviewers used Digitaliser v11.1 [Engauge] to calculate the exact pain intensity based on the charts in studies. Meanwhile, reviewers only included parallel RCTs, in which initial evidence hierarchy was considered as “high” [30]. RCTs with a high risk of bias were excluded by the use of Cochrane risk of bias tool in any domain. Reviewers only included RCTs reported in the English language. There were no restrictions on the year of publication. Finally, reviewers excluded unpublished or ongoing RCTs in international trial registers because the quality of these studies was not completely clear.

Identification of studies

For this NMA, reviewers searched PubMed, Cochrane Library and Embase for RCTs published from the date of database inception to 27 October 2019 using MeSH terms and keywords. The search strategy was presented in detail in supplement file 1.

Two reviewers (HR and JL) independently screened titles and abstracts of the search results to exclude irrelevant studies and duplicate studies. Then YL and CY included studies that met the criteria by reading full-text and recorded this process. Their differences were resolved through discussion, which was joined by a third review author (HR). Finally, reviewers (HR and JL) assessed the risk of bias of all included studies with the Cochrane risk of bias tool. This tool covers the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Disagreements were resolved by discussion.

Data extraction

Two reviewers (HK and GB) independently extracted and summarized the data using a predesigned extraction table. The extracted information included general information, participants, interventions and outcomes. Discrepancies within the data abstracted were typically resolved by duplicate extraction and discussion; however, a third reviewer (HR) was consulted when an agreement could not be reached.

Outcomes Assessed

Pain reduction, evaluated with the VAS scores, was the main evaluation index. Reviewers calculated effect sizes by determining mean difference (MD) and corresponding 95% confidence interval (CI).

Network meta-analysis

All statistical analyses were performed using STATA via the mvmeta package. In network meta-analysis, reviewers evaluated transitivity by considering the similarity of participants, interventions, outcomes measurements, and trial methodologies. Meanwhile, reviewers used the node-splitting method to assess model inconsistency (ie, the agreement between direct and indirect evidence) [31]. If the statistical test of the difference between direct comparison and indirect comparison was statistically significant ($p < 0.05$), reviewers accepted the inconsistency between direct comparison and indirect comparison. To provide a numerical ranking of the association between all interventions and pain reduction, the reviewers used a surface under the cumulative ranking curve (SUCRA). A higher SUCRA demonstrates better effects for the respective intervention [32]. Reviewers also drew funnel plots to detect the presence of potential publication bias by checking the symmetry of the funnel plots [32]. Network plot, forest plot, ranking plot, and funnel plot were completed through the use of network commands. After evaluating these results, reviewers created a summary table of survey results using the GRADE system according to methods developed by the GRADE working group [33].

Results

Eligible studies

The search strategy yielded 395 potentially relevant articles. After removing duplicates, there were 286 studies. Then 55 potentially eligible articles were obtained by screening the titles and abstracts carefully. After careful full-text screening and assessment of the risk of bias, 20 RCTs met the inclusion criteria [4,

10, 12, 15, 28, 34-48]. This selection process and exclusion reasons were presented in the flow chart (Fig. 1). These studies, published between 2006 and 2019, included 758 TMD patients, which consisted of 358(47.23%) for LLLT, 73(9.63%) for TENS, and 327(43.14%) for placebo. 494 of 758 participants were women and 162 were unclear. The search results contained 20 direct comparisons, of which 17 were LLLT versus placebo, two were TENS versus placebo, one was LLLT versus TENS, and one was LLLT versus TENS versus placebo. Then the one-month follow-up network contained seven RCTs, including six comparisons of LLLT and placebo and one comparison of LLLT, TENS and placebo. The numbers of participants in these studies were 246. Ten (50%) of all included trials recruited patients from Brazil, four (20%) from Italy, three (15%) from Turkey, two (10%) from Iran, and one (5%) from Austria. Among 14 trials, the average participant was 14-76 years old, and the ages of the others were not mentioned.

Risk of bias assessment

Quantification of the risk of bias assessment was presented in Fig. 2. A random sequence was adequately generated with the help of a computer program or a random number list in five studies, and the risk of bias in the domain of randomization was judged to be 'low'. Allocation concealment was classified as an unclear risk in 17 studies because of no specific reporting of allocation concealment. The participants and personnel were successfully blinded in most studies (n=13, 65%), and the risk of bias was judged to be 'low'. Other studies without similar reports were rated as unclear risk of bias in this domain. As for blinding of outcome assessment, most studies were rated as a low risk of bias (n=15, 75%). Reviewers argued that the outcome assessment was unlikely to be influenced as long as the participants were blind since the pain intensity was assessed by the participants. All studies were determined to have a low risk of bias for the incomplete outcome data element because the information stemmed from studies with a low risk of bias, and there were no missing data. Besides, reviewers rated all studies as low risk of reporting bias and other bias. Because the pre-specified outcomes in the studies were reported, and no other significant bias problems were found.

Results of the network meta-analysis

Figure 3 showed two network plots for the pain reduction immediately after the final treatment and a month after therapy finalization. The size of the circle and the thickness of the edge were proportional to the number of participants and studies, respectively. Connecting lines represented direct comparisons between the two connected interventions, while the intervention pairs without connection can be compared indirectly through a network meta-analysis. Reviewers identified transitivity between studies after taking into account similarities among participants, interventions, outcomes measurements, and trial methodologies. The node-splitting method found no inconsistency because the statistical test of the difference for each group was not statistically significant ($P>0.05$).

According to the results of network meta-analysis, LLLT and TENS were associated with significantly lower pain intensity compared with placebo immediately after treatment [MD=1.99,95%CI:(1.07,2.92);MD=2.16,95%CI:(0.27,4.04),respectively]. However, there was no statistically significant difference between LLLT and TENS [MD =0.16, 95%CI:(-1.79,2.11)]. As for pain reduction one month after

treatment, statistical significance was observed only for LLLT when compared with the placebo [MD=1.74, 95% CI: (0.02, 3.46)]. No statistically significant differences were found for placebo versus TENS or LLLT versus TENS [MD=1.54, 95%CI:(-2.26,5.35); MD=-0.20,95%CI:(-4.00,3.61), respectively].

The ranking probability of each intervention in terms of two periods of time was illustrated in Fig. 4. The possibilities of LLLT, TENS being the best intervention were 43.7%, 56.3% (immediately after treatment) and 53%, 45.5% (one month after treatment). And placebo always ranked the last.

Across the network, reviewers considered that three comparisons (A vs B, B vs C, A vs C, A, B, and C were used to describe the LLLT, placebo, and TENS respectively) were of low quality immediately after treatment. Due to the inconsistency or imprecision or both in the results, the confidence of the evidence in the studies was moderate or low. Meanwhile, reviewers found that there was a typical asymmetry in the funnel plot, which was mainly reflected in the fact that the studies on the left side of the mean effect size were much more than those on the right side, indicating potential publication bias. So, reviewers rated down all the direct and indirect comparisons. From the evidence after a month of therapy completion, one comparison (B vs A) was rated as “moderate”, and the other two comparisons (B vs C, A vs C) were rated as “low”. No publication bias was identified among these pairwise comparisons. Reviewers incorporated the GRADE judgments in Table 1. All the reasons for downgrading were labelled.

Discussion

Summary of Evidence

The present network meta-analysis compared the effectiveness of LLLT and TENS in reducing overall pain intensity perceived by TMD patients. We considered that the final data favored LLLT over TENS, which may be in part due to the following reasons. As for pain reduced at the end of therapy, TENS ranked first in SUCRA ranking category, followed by LLLT, with little difference between the two interventions. And the point estimates of “B vs A” and “B vs C” were calculated as 1.99 and 2.16, respectively. That meant the two treatments promoted pain relief similarly and were more remarkable than placebo. However, the 95% CI of “A vs C” in pain reduction included “0”, and there was no statistical evidence, either LLLT or TENS worked better. For pain relief one month after treatment, LLLT ranked the first with the highest SUCRA score. Compared with placebo, the common comparator, LLLT promoted more suitable effects (point estimate=1.74). Also, both comparisons of the 95% CIs regarding TENS in pain reduction included “0”, these differences didn’t reach the point of statistical significance. Therefore, these data suggested that LLLT can be accepted as a more appropriate treatment modality in the relief of short-term painful TMD, when compared with TENS.

The study by Kato.et al. [10] and Seifi.et al. [12] revealed that both LLLT and TENS caused a noticeable decrease in painful symptoms for the short term, which may account for the cumulative effect. Nunez.et al. [14] supported that LLLT was more efficient than TENS in improving the amplitude of mandibular movement. We combined direct and indirect evidence to further clarify LLLT was the better choice in this network meta-analysis. The study reported that laser is a kind of electromagnetic radiation source with

particular properties, including monochromaticity, coherence, directivity, brightness and polarization [49]. These properties allow specific doses of energy to be delivered to target tissues without the need for incisions in the skin [50]. LLLT is a photochemical effect, similar to photosynthesis in plants, in which light is absorbed and produces chemical changes, and that is completely different from the ablative or thermal mechanisms of other medical laser procedures [9]. Meanwhile, LLLT can be applied to treating a variety of conditions, including damaged wound, pain and inflammation [14]. Although TENS is easier to use than LLL because of its small size, low risk, and convenient portability, the current delivered to the skin through TENS may make some patients uncomfortable [12]. Some experts observed that patients were easy to accept LLLT during the treatment process because LLLT does not emit heat, sound, vibration or light in the infrared spectrum, making it indistinguishable from placebo therapy. So, the improvement of their pain symptoms might also have a psychological effect, which was reflected in the VAS values [37]. More and larger trials are needed to confirm this in the future.

Strengths and limitations of this study

This study has some advantages. It is the first network meta-analysis to compare the efficacy of LLLT and TENS in the treatment of pain caused by TMD. Previous studies used several RCTs to analyze the effectiveness of LLLT and TENS, and it was still under debate. In our study, we combined direct evidence with indirect evidence to increase the credibility of evidence by comparing LLLT or TENS or placebo group. Meanwhile, we evaluated better treatment options in combination with data on pain relief immediately after treatment and at the one-month follow-up. We applied reliable methods as recommended by Cochrane collaboration and GRADE for network meta-analysis. SUCRA ratings of outcomes were used to distinguish subtle differences between the two treatments. Finally, we showed that choosing LLLT in TMD management may be beneficial in patients to achieve better efficacy.

Nevertheless, our results should be interpreted with caution because the study has several shortcomings. First, According to the GRADE framework, the quality of many comparisons was assessed as low quality, which largely restricts the interpretation of these results. The inconsistency and imprecision of the results, as well as publication bias, existed in our network. Differences in parameters such as wavelength, power output and pulsing frequency, or in numbers and frequencies of treatment sessions, as well as the low number of studies on TENS, hindered some comparisons between studies, and affected the certainty of the meta-analysis results. Several studies did not report the used parameters, which caused difficulties in making subgroup analysis. Therefore, further research is strongly encouraged to establish optimal and uniform parameters. Meanwhile, potential publication bias could not be eliminated. We only included published RCTs instead of some unpublished grey literature. We tried our best to solve this limitation only by downgrading the quality in GRADE. As mentioned, more relevant, high-quality clinical RCTs are required to improve the credibility in the future. Second, the results of LLLT and TENS in our meta-analysis are restricted to pain relief assessment during one-month follow-up owing to limited data in our literature. We believe that the choice of outcome measurement is reasonable in theory because pain is the most common cause of TMD patients asking for medical help. Additional studies should be conducted to investigate the long-term effects and functional outcomes. Third, our study covered a variety of TMD

including muscle origin, joint origin, or both, which reduced the level of conclusion due to insufficient description of TMD types in some studies. In addition, given the complex nature of TMD, the multifactorial pathogenesis should be considered. This study only discussed two physical therapies for attenuating the signs and symptoms of pain in TMD, which has certain limitations. LLLT can be used as an important noninvasive treatment to reduce pain and actively help patients to resume their daily activities. However, there is no doubt that a combination of several therapeutic approaches may be a more appropriate treatment.

Conclusion

The present meta-analysis compared the effectiveness of LLLT and TENS for treating TMD. Regarding the two follow-up time points, LLLT provided relatively more effective pain relief compared with TENS for the short-term. Therefore, more studies are needed to determine long-term efficacy in the future.

Abbreviations

LLLT:low-level laser therapy; TENS:transcutaneous electric nerve stimulation; TMD:temporomandibular joint disorders; RCTs:randomized controlled trials; VAS:visual analogue scale; MD:mean difference; CI:confidence interval; TMJ:temporomandibular joint; SR:systematic review; NMA:network meta-analysis; SUCRA:surface under the cumulative ranking curve.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

HR, GB and HK finished study design and relative studies search. JL, YL, CY and HR conducted study selection and the assessment of the risk of bias. HK, GB and HR finished data extraction. HR did the data analysis. All reviewers drafted and revised the manuscript. All reviewers agreed with the final results and conclusions.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, Tables 1 & 2 are only available for download from the Supplementary Files section.

Figures

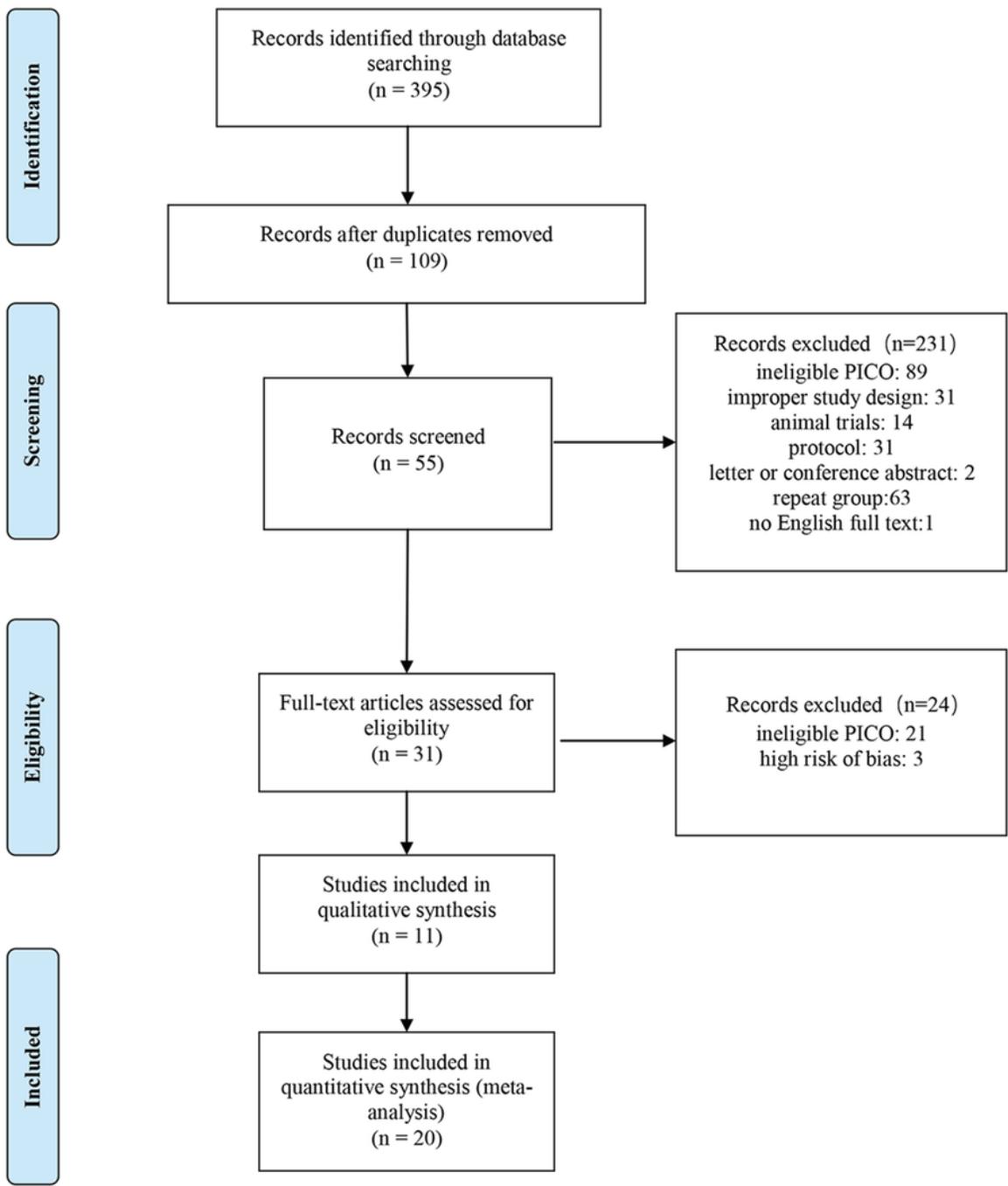


Figure 1

PRISMA diagram

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Borges, R. M. M 2018	+	?	+	+	+	+	+
Carrasco, T. G 2008	?	?	+	+	+	+	+
Çetiner, S 2006	?	?	?	?	+	+	+
Costa, Sap 2017	?	?	+	+	+	+	+
Cunha, La 2008	?	?	?	?	+	+	+
da Silva, M. A. 2012	?	?	+	+	+	+	+
De Giorgi, I. 2017	?	?	?	+	+	+	+
Del Vecchio, A. 2019	+	+	+	+	+	+	+
Demirkol, N. 2015	?	?	?	?	+	+	+
Emshoff, R. 2008	+	?	+	+	+	+	+
Ferreira, A. P. 2017	+	+	+	+	+	+	+
Fornaini, C. 2017	?	?	?	+	+	+	+
Kato, M. T. 2006	?	?	+	+	+	+	+
Leal, De Godoy Ch 2015	?	+	+	+	+	+	+
Madani, As 2014	?	?	+	+	+	+	+
Marini, I. 2010	?	?	+	+	+	+	+
Mazzetto, M. O. 2010	?	?	?	?	+	+	+
Mazzetto, Mo 2007	?	?	+	+	+	+	+
Sancakli, E 2015	+	?	+	+	+	+	+
Seifi, M. 2017	?	?	?	?	+	+	+

Figure 2

Risk of bias summary

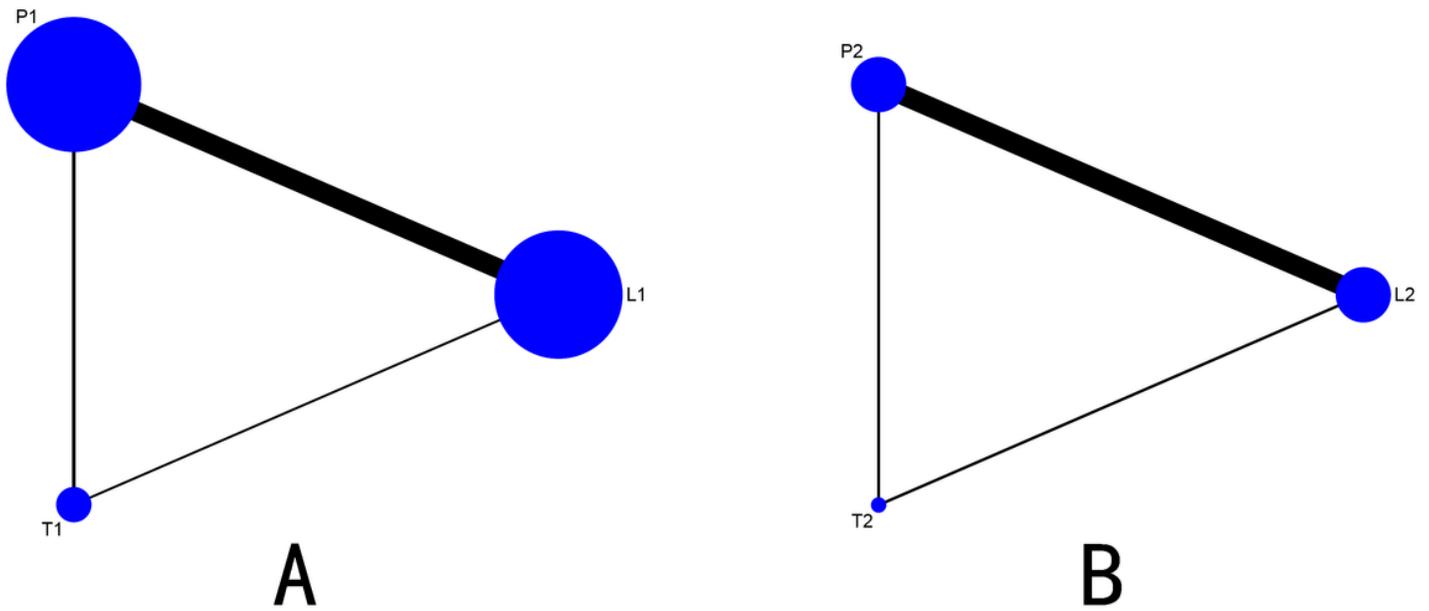


Figure 3

Network plot Note: (A) immediately after treatment (B) one month after treatment L: LLLT P: placebo T: TENS

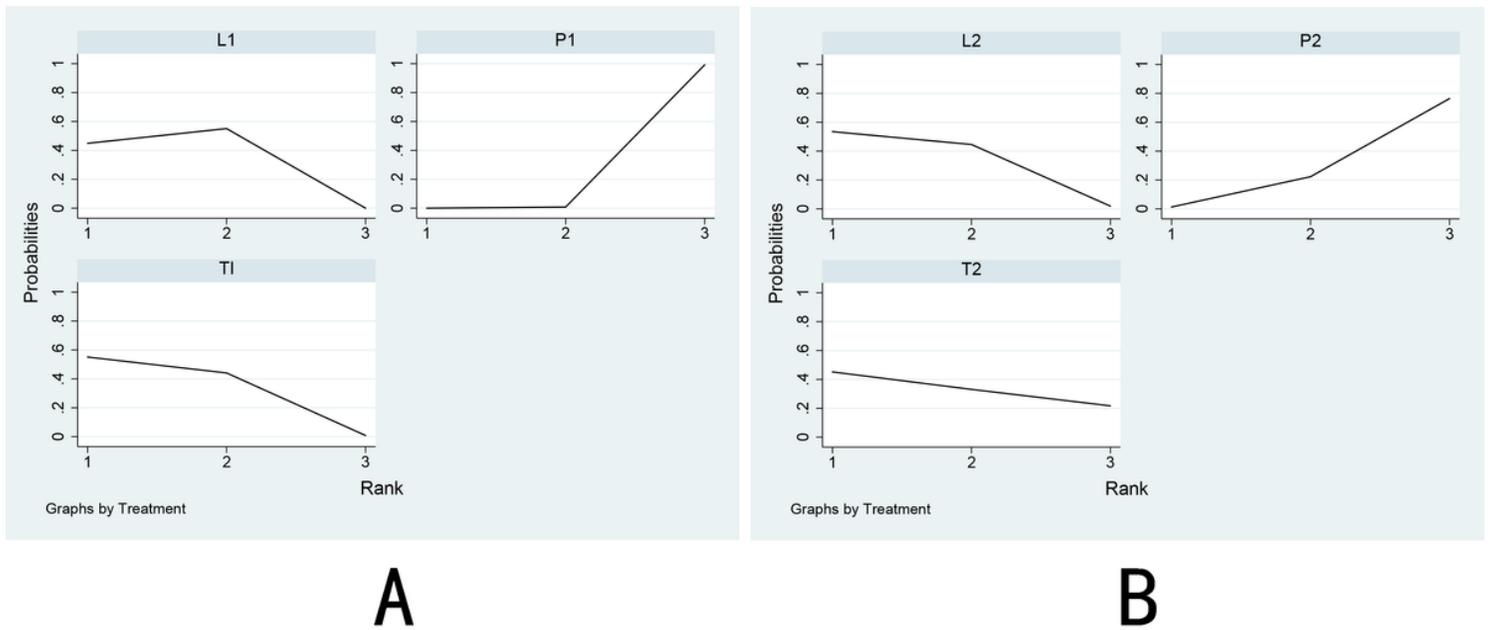


Figure 4

SUCRA rank plot Note: (A) immediately after treatment (B) one month after treatment L: LLLT P: placebo T: TENS

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.Searchstrategy.pdf](#)
- [table1and2.docx](#)