

Comparison of the Efficacy of Dextrose Prolotherapy in Lateral Elbow Tendinopathy: A Systematic Review and Meta-Analysis of Randomized Controlled trials

Chernkhuan Stonsaovapak^{1,2} and Natthiya Tantisiriwat^{1,2}

¹Department of Rehabilitation Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, ²Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

ABSTRACT

Objectives: To compare the efficacy of dextrose prolotherapy (DPT) and alternative treatments for lateral elbow tendinopathy (LET) patients.

Study design: A systematic review and meta-analysis.

Setting: Not applicable.

Subjects: Patients in all stages of LET.

Methods: The authors searched databases of studies that compared the efficacy of DPT to alternative treatments for LET published in PubMed and Scopus from 1 January 2001 to 20 April 2021. The primary outcomes were the visual analog scale for pain (VAS) at rest and during movement. Secondary outcomes included pain-free grip strength, Quick Disabilities of the Arm, Shoulder and Hands (QuickDASH) scores, and Patient-Rated Tennis Elbow Evaluation (PRTEE) scores. The data, provided as means and standard deviations, were converted to standardized mean differences (SMD) with 95% confidence intervals (CI). The Review Manager 5.3 Software, Risk of Bias 2, and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) were used for data analysis, risk of bias assessment, and quality assessment.

Results: Six randomized controlled trials (RCTs) which met the eligibility criteria were included. In each of those trials, the DPT group had significantly reduced VAS pain scores at rest and during movement at 12 weeks post-treatment compared to the other treatment groups. In terms of function improvement, the DPT group also had significantly greater improvement in QuickDASH scores than the other treatment groups at 12 weeks. However, these positive findings were based on methodologies which had a moderate to high risk of bias and were underpowered.

Conclusions: DPT requires additional high-quality RCTs to determine the benefits to patients with LET. The main reason for the inconclusive results in this study was that most of the reviewed RCTs demonstrated a moderate to high risk of bias.

Keywords: dextrose prolotherapy, lateral epicondylitis, regenerative medicine, tennis elbow, treatment

ASEAN J Rehabil Med. 2022; 32(1): 2-10.

Introduction

Lateral elbow tendinopathy (LET) or tennis elbow is considered a common musculoskeletal pain disrupting normal daily functions and work activities. There are various alternative treatments for LET, including non-invasive and invasive management. The non-invasive treatments are usually the initial approaches and include “wait and see,” elbow splint, physical modalities, exercise of wrist extensor muscles, and pain-relieving medications.¹ Some patients for whom non-invasive treatment failed are still suffering due to their pain. Practitioners caring for those patients should provide other options to help alleviate pain. Intervention procedures, including injection of corticosteroid, botulinum toxin, autologous blood products, hyaluronic acids, and prolotherapy, should also be considered.²⁻⁴

Recent discoveries about the pathophysiology of LET have revealed it to be a degenerative, rather than an inflammatory, process.^{5,6} This has been confirmed by a meta-analysis showing that corticosteroids do not provide benefits in pain relief or improved function in patients with enthesopathy of the extensor carpi radialis brevis in the short-, intermediate-, or long-term when compared to a placebo.⁷ Studies in regenerative medicine have provided a growing body of data regarding treatment of tendinopathy. In the area of pain reduction, several meta-analyses have reported that the long-term effects of Platelet-Rich Plasma (PRP) and autologous blood injection are superior to corticosteroid injections,^{2,3,8} however, this finding has been questioned in a recently published meta-analysis comparing PRP with a placebo injection.⁹ Another treatment, extracorporeal shockwave therapy (ESWT), which involves the application of regenerative mechanisms, has been reported to show efficacy in both pain and disability reduction;^{10,11} however, the treatment is expensive and may be beyond the financial resources of some developing countries.

Prolotherapy, which uses a regenerative mechanism without biologic agents, is gaining interest for treatment of

Correspondence to: Chernkhuan Stonsaovapak, MD, FRCPhysiatrT; Department of Rehabilitation Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society Bangkok 10330, Thailand; E-mail: chernkhuan@gmail.com

Received: 22nd July 2021

Revised: 16th August 2021

Accepted: 30th August 2021

chronic tendinopathy. Hypertonic dextrose (10-20% dextrose) is one of the substances commonly injected in prolotherapy. Dextrose prolotherapy (DPT) produces an inflammatory response and stimulates fibroblast proliferation which accelerates the healing process.¹² In recent years, meta-analyses have described the efficacy of DPT in common chronic musculoskeletal problems such as knee osteoarthritis and tendinopathy.¹³⁻¹⁵ DPT is a low-cost, easily accessible, and non-toxic treatment, accessible even to patients in low- and middle-income countries.

The efficacy of DPT for LET has been studied in a randomized controlled trial (RCT) comparing a variety of arms categorized into two groups: a non-active control group ("wait and see" treatment or placebo saline injection) and an active control group (physiotherapy, corticosteroid injection, hyaluronic acid injection, and radial ESWT).¹⁶⁻²¹ The present study aimed to compare the efficacy of DPT with other treatments for patients with LET.

Methods

The present study was conducted following PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines.

Inclusion and exclusion criteria

Inclusion criteria for this study were set based on the Population, Intervention, Control, Outcomes (PICO) framework as follows: (1) population: all stages of LET patients (2) intervention: dextrose prolotherapy, (3) control: any other comparators e.g., other treatments, placebo, "wait and see", (4) outcomes: pain scores and functional outcomes, (5) study design: RCTs. The exclusion criteria were: (1) articles not written in the English language, (2) articles which did not report major outcomes or which lacked data, (3) studies which included participants who had arthritis or connective tissue disease, e.g., rheumatoid arthritis.

Data sources

The search for randomized controlled trials was conducted using the PubMed and Scopus electronic databases for the period 1 January 2001 to 20 April 2021. The present study was registered with the International Prospective Register of Systematic Reviews (PROSPERO). The registration (CRD42021258117) is available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258117.

Search strategy

Keywords used during searches included the following: (((tennis elbow) OR (lateral epicondylitis) OR (lateral elbow pain) OR (lateral humeral epicondylitis) OR (lateral epicondylalgia)) AND ((dextrose) OR (prolotherapy) OR (injection))) AND ((randomized controlled trial [Publication Type] OR (randomized [Title/Abstract] AND controlled [Title/Abstract] AND trial [Title/Abstract]))).

Selection process

Covidence systematic review software²² was used in screening for titles and abstracts compatible with the study criteria. Two reviewers independently reviewed the articles identified in the literature search. Duplicate articles were identified and excluded. Eligible articles were selected based on adherence to the inclusion and exclusion criteria. Disagreements regarding enrollment eligibility of articles were discussed and resolved by the two reviewers.

Data collection process

The two reviewers independently extracted data from each of the articles. Discrepancies in the extracted data were evaluated and rechecked. Extracted items included background information, e.g., study design, number of participants, baseline characteristics of the participants, as well as details of the intervention and comparators, outcomes assessment, and follow-up timing. The primary outcome of interest was the pain scores, e.g., Visual Analogue Scale (VAS) pain score ratings at rest and during movement. Secondary outcomes included functional outcomes, e.g., pain-free grip strength (PFG) (newton-force values were converted to kilogram-force), Quick disabilities of the arm, shoulder and hands (QuickDASH) scores and Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire scores.

In assessing the effects of treatment, in this study short-term effects were defined as data recorded at between 4 and 12 weeks after the interventions. Intermediate effects were defined as effects recorded at more than 12 weeks but less than 24 weeks. Outcome data reported as median and range in the original article were converted to mean and standard deviation for data synthesis and analysis.^{23,24} Missing standard deviations of changes from baseline were imputed using imputed correlation coefficient values.²⁵ PFG data in some articles were represented as a ratio; in those cases, the authors contacted the authors of those articles who were available to clarify the data.

Risk of bias and quality assessment

The authors used the Risk of Bias 2 (RoB 2) tool²⁶ for the risk of bias assessment which included the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of reported results. Both reviewers independently rated the bias concerns, giving a score of "Low concern", "Some concern", or "High concern" for each item. Risk of traffic light plot and summary plot bias were generated using Risk-Of-Bias Visualization (robvis).²⁷

In rating the quality of the evidence, the authors worked independently using Grading of Recommendations Assessment, Development and Evaluation (GRADE).²⁸ A final consensus was reached through discussion.

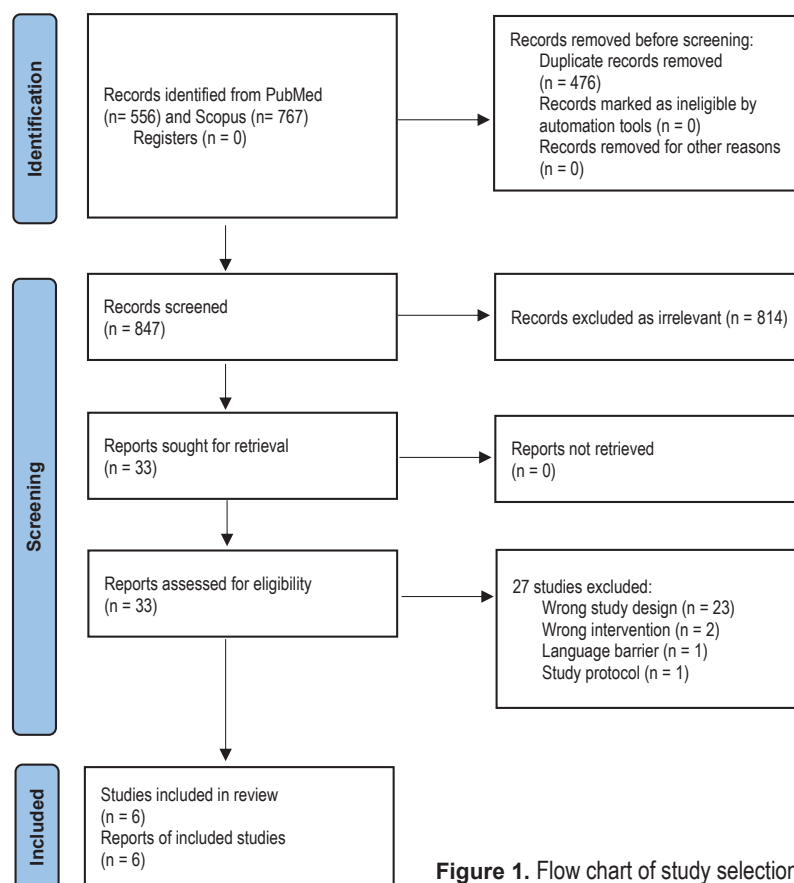


Figure 1. Flow chart of study selection.

Table 1. Characteristics of included studies

Study	Year	Design	Number of subjects		Age (years) ¹		Female (%)		Onset (months) ¹	
			DPT	Control	Control		DPT	Control	DPT	Control
Rabogo et al.	2013	RCT	10	12	50.4 (6.8)	51.7 (6.8)	14.0	40.0	61.7 (48.2)	55.5 (73.4)
Yelland et al.	2019	RCT	40	40	49.2 (7.2)	51 (9)	45.0	40.0	5.8 (4.07)	5.25 (6.37)
Bayat et al.	2019	RCT	14	14	46.2 (6.4)	50.7 (7.5)	43.0	79.0	5.7 (2.5)	10.3 (8)
Ahadi et al.	2019	RCT	17	16	46.7	47.3	64.7	75.0	6.82 (5.73)	4.13 (1.48)
Akcay et al.	2020	RCT	27	23	48.1 (8.9)	46.7 (8.3)	78.3	70.4	21 (32.81)	12 (4.76)
Apaydin et al.	2020	RCT	16	16	43.3 (7.4)	45.6 (4.7)	81.3	81.3	> 6	> 6

¹Mean (SD); SD, standard deviation; DPT, dextrose prolotherapy; RCT, randomized control trial

Statistical methods

The authors used Review Manager (RevMan) 5.3 software for data analysis. Continuous data that were originally presented as means and standard deviations were converted to standardized mean differences (SMD) and 95% confidence intervals. Statistical significance was set at p -value < 0.05. The I^2 statistic was used to analyze the heterogeneity of the data which was categorized as follows: low heterogeneity (25-50%), moderate heterogeneity (50-75%), high heterogeneity (greater than 75%). For outcomes with high heterogeneity, a random-effects model was used.

Results

Study selection

Searches of the literature databases identified 1,323 potential studies from which a total of 476 duplications were removed. After screening the remaining titles and abstracts

following the PICO model (population, intervention, control, and outcomes), 33 studies were selected for inclusion in a comprehensive review. Two studies which had used a combination of sclerotic agents in addition to dextrose, e.g., sodium morrhuate, phenol, and glycerine were excluded.²⁹⁻³⁰ Finally, six articles¹⁶⁻²¹ which met the study eligibility criteria were included in the meta-analysis. Figure 1 shows the flow of study selection.

Study characteristics

All six of the included articles, all published between 2013 and 2020, were RCTs. In those studies, a combined total of 124 patients were enrolled in the DPT group with an additional 121 patients in the comparator group. The demographics of the participants and general information about the included studies are shown in Table 1 and Table 2, respectively.

Table 2. Summary of interventions, comparators, outcome assessment details and GRADE assessment of the included RCTs

Study	DPT (percentage of concentration of dextrose): cocktail solutions [total volume per dose]	Comparators	Total DPT injection sessions (timing of injections)	Injection technique	Outcomes	Follow-ups (weeks)	Quality of the evidence (GRADE)
Rabogo et al. 2013	DPT 20%: 4 mL 50% dextrose + 4 mL 0.9% saline + 2 mL 1% lidocaine [10 mL]	Wait and see	1	US guided injection with a peppering technique	PFG, PRTEE, MRI-based severity scores	4,8,16,32	Low
Yelland et al. 2019	DPT 20%: 20 % glucose and 0.4% lignocaine [0.5-1 mL per tender point, total does not exceed 5 mL]	Physiotherapy (education, manual therapy and therapeutic exercise was used in conjunction with a home exercise program)	4 (0,4,8,12 week)	Blinded injection with a peppering technique	NRS at rest, PFG, PRTEE, GIC, EuroQoL EQ-5D-3L scored	6,12,26,52	High
Bayat et al. 2019	DPT 16%: 2.5 mL dextrose 20% and 1 mL lidocaine 2% [3 mL]	Steroid: 1 mL methylprednisolone 40 mg/mL and 2 mL of 1% lidocaine (total volume 3 mL)	1	Blinded injection with a peppering technique	VAS at rest, QuickDASH	4, 12	Low
Ahadi et al. 2019	DPT 20%: 3 mL of 20% dextrose [3 mL]	Radial ESWT (2000 shots, intensity 1.5 bars, 10 Hz; 3 sessions with a weekly interval)	1	Blinded injection	VAS at rest, PFG, Pain pressure threshold, QuickDASH	4,8	Moderate
Akcaay et al. 2020	DPT 15%: 15% dextrose [1.5 mL]	1.5 mL of saline (0.9% NaCl)	1	Blinded injection	VAS at rest, VAS during action, PFG, PRTEE, DASH	4,8,12	Low
Apaydin et al. 2020	DPT 15%: 1 mL of 2% lidocaine, 5 mL of 30% hypertonic dextrose, and 4 mL of 0.9% isotonic [5 mL]	Hyaluronic acid: a single dose of 30 mg/2 mL 1500 kDa high-molecular-weight	3 (0,3,6 week)	Blinded injection with a peppering technique	VAS at rest, VAS during action, PFG, QuickDASH	6,12	Moderate

DPT, dextrose prolotherapy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; US, ultrasound; PFG, pain-free grip strength; PRTEE, Patient-Rated Tennis Elbow Evaluation; MRI, magnetic resonance imaging; NRS, numeric rating scale; GIC, Global Impression of Change; EQ-5D-3L, EQ-5D three-level version; VAS, Visual Analogue Scale; ESWT, Extracorporeal Shockwave Therapy; QuickDASH, Quick disabilities of arm, shoulder and hands

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Rabogo et al.	-	+	+	X	+
	Yelland et al.	+	+	+	+	+
	Bayat et al.	-	-	+	+	+
	Ahadi et al.	-	+	-	+	+
	Akcay et al.	+	X	-	+	+
	Apaydin et al.	-	+	+	-	+
		Domains:				
		D1: Bias arising from the randomization process.				
		D2: Bias due to deviations from intended intervention.				
		D3: Bias due to missing outcome data.				
		D4: Bias in measurement of the outcome.				
		D5: Bias in selection of the reported result.				
		Judgement				
		X High				
		- Some concerns				
		+ Low				

Figure 2. Summary of risk of bias assessment of the included study

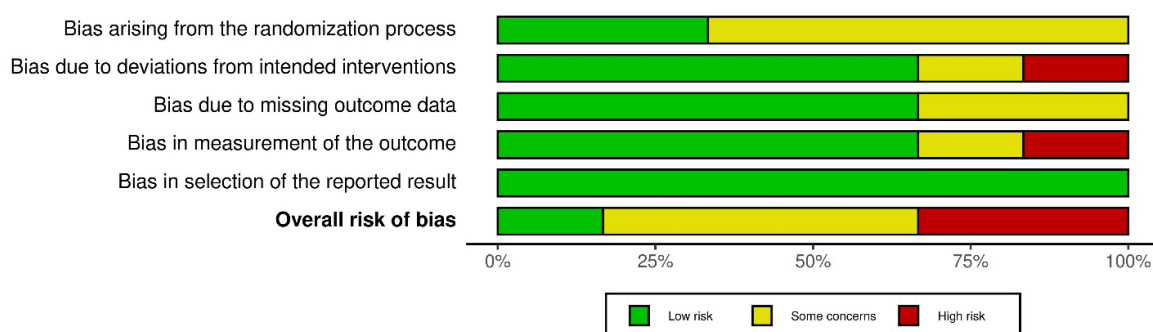


Figure 3. Risk of bias summary

Risk of bias and quality assessment

Only two articles described the allocation concealment process used.^{17,20} One study had a high risk of bias in the domain of deviations from intended intervention detected using per-protocol analysis despite a larger than five percent drop-out rate among the prolotherapy group.²⁰ Two studies raised some concerns regarding bias in missing outcome data.^{18,20} One study did not blind the assessor which could potentially have influenced participant-reported outcomes resulting in a high risk of bias in the domain of measurement of the outcome.¹⁶ There was a low risk of bias in the selective report of the outcome of all included articles. (Figures 2 and 3). In summary, the study of Yelland et al.¹⁷ demonstrated a low risk of bias whereas the others evidenced a moderate to high risk of bias. Quality assessment with GRADE revealed that Yelland et al.¹⁷ had a high quality of evidence compared to the low-to-moderate quality in the other studies which was primary due to their higher risk of bias and their small sample size which can lead to imprecision.

Clinical outcomes

Pain VAS at rest

Four studies¹⁸⁻²¹ reported the short-term effects (ranging from 4 to 6 weeks) (Figure 4A) and three studies¹⁹⁻²¹ mentioned the intermediate-term effects (at 12 weeks) of the pain VAS at rest for DPT versus other comparators (Figure

4B). The results showed that DPT significantly reduced pain scores in the intermediate term (SMD, -0.62; 95% CI [-1.00 to -0.23], $P = 0.002$, $I^2 = 0\%$) (Figure 4B). However, there was no statistically significant difference in the short-term effects (SMD, 0.18; 95% CI [-0.54 to 0.90]; $P = 0.62$; $I^2 = 77\%$) (Figure 4A).

Pain VAS during movement

Two studies reported pain VAS during motion in the short term (4 to 6 weeks) (Figure 5A) and the intermediate term (at 12 weeks)(Figure 5B).^{20,21} The results showed that DPT significantly reduced pain scores in the intermediate term (SMD, -0.80; 95% CI [-1.30 to -0.29]; $P = 0.002$; $I^2 = 17\%$; Figure 5B). However, there was no significant difference in the short-term effects. (SMD, -0.37;95% CI [-0.81 to 0.07]; $P = 0.10$; $I^2 = 0\%$; Figure 5A).

Pain-free grip strength

Four studies^{16-18,21} reported PFG effects in the short term (4 to 8 weeks) and three studies^{16,17,21} reported intermediate-term effects (12 to 16 weeks). Two studies^{17,20} reported PFG as an affected/unaffected ratio, but only one study provided the raw PFG data for the affected side alone.¹⁷ There was no statistically significant difference between DPT and other comparators in the short-term and intermediate-term effects on PFG. ((SMD, -0.13; 95% CI [-0.73 to 0.48]; $P = 0.68$; $I^2 = 71\%$; Figure 6A), (SMD, 0.27;95% CI [-0.95 to 1.48]; $P = 0.67$; $I^2 = 90\%$; Figure 6B)).

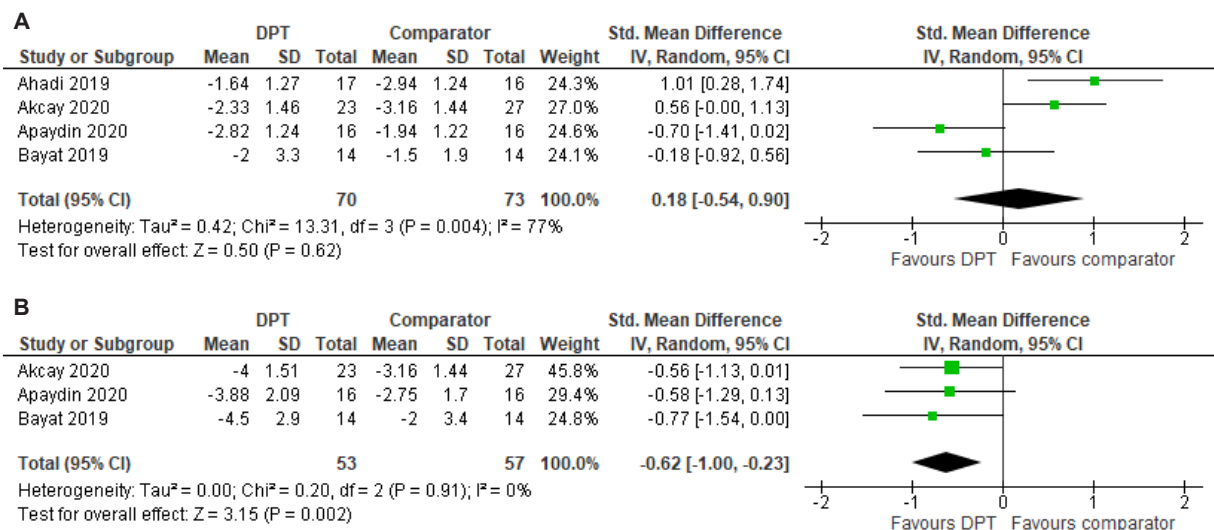


Figure 4. Forest plot of pain VAS at rest in the short (A) and intermediate term (B)

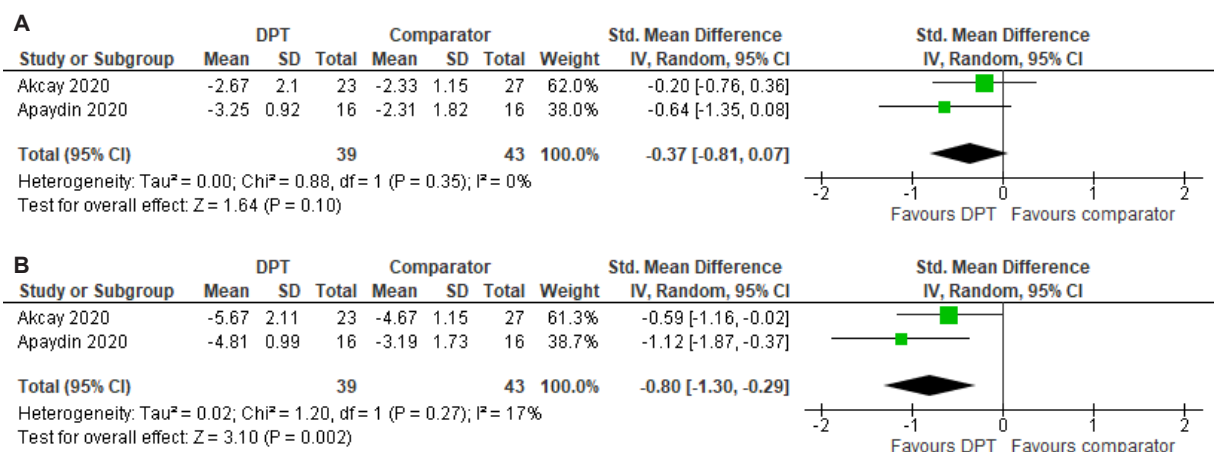


Figure 5. Forest plot of pain VAS during movement in the short (A) and intermediate term (B).

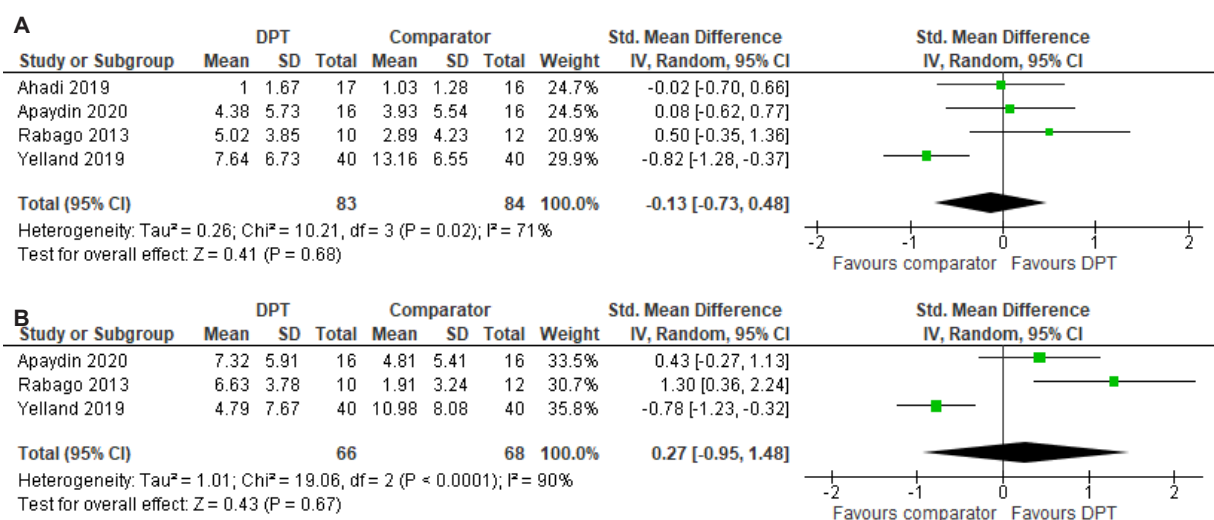


Figure 6. Forest plot of pain-free grip strength in the short (A) and intermediate term (B)

Quick disabilities of arm, shoulder, and hands (QuickDASH)

Three studies^{18,19,21} reported QuickDASH outcomes in the short term (4-6 weeks) (Figure 7A) and two studies^{19,21} reported outcomes in the intermediate term (at 12 weeks) (Figure 7B). One RCT used DASH instead of QuickDASH,

so that outcome was excluded from our study.²⁰ The results revealed that DPT could improve QuickDASH scores better than the other treatments (steroid and hyaluronic injections) in the intermediate term. (SMD, -1.30; 95% CI [-1.86 to -0.73]; $P < 0.001$; $I^2 = 0\%$; Figure 7B) However, the short-term effects as measured by QuickDASH scores demonstrated no

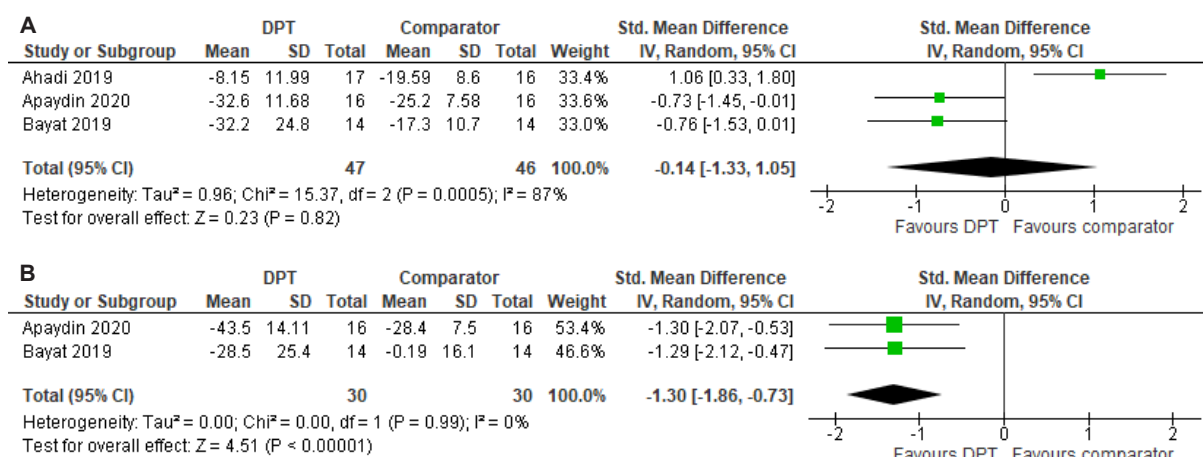


Figure 7. Forest plot of QuickDASH in the short (A) and intermediate term (B)

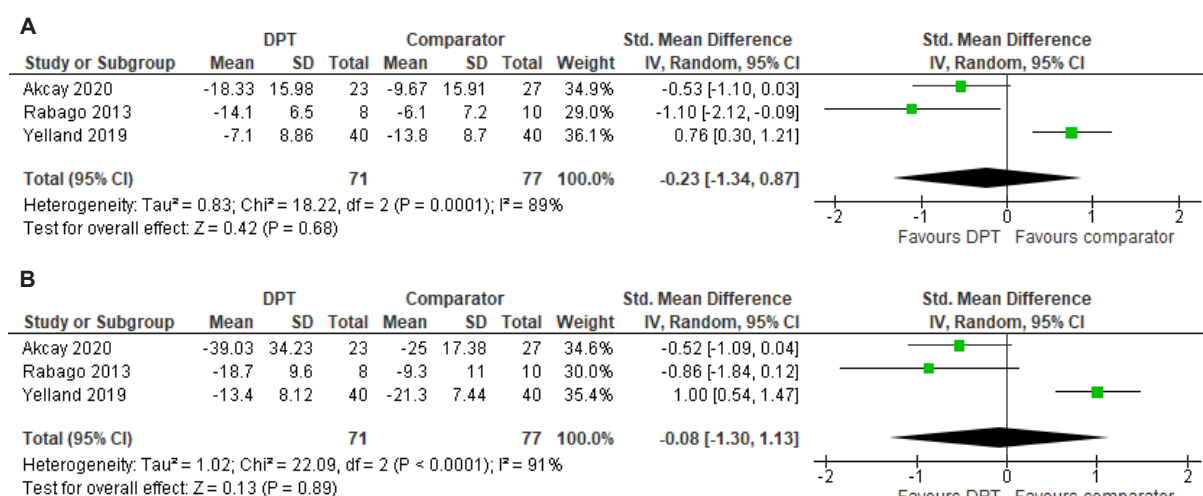


Figure 8. Forest plot of PRTEE in the short (A) and intermediate term (B)

statistically significant difference. (SMD, -0.14; 95% CI [-1.33 to 1.05]; $P = 0.82$; $I^2 = 87\%$; Figure 7A)

Patient-Rated Tennis Elbow Evaluation (PRTEE)

Three studies^{16,17,20} evaluated the effects of PRTEE in the short term (4 to 6 weeks) and in the intermediate term (12 to 16 weeks). The results revealed no statistically significant difference between DPT and other comparators in PRTEE outcome at any of the assessment points. ((SMD, -0.23; 95% CI [-1.34 to 0.87]; $P = 0.68$; $I^2 = 89\%$; Figure 8A), (SMD, -0.08; 95% CI [-1.30 to 1.13]; $P = 0.89$; $I^2 = 91\%$; Figure 8B)).

Discussion

A comprehensive review of evidence related to the efficacy of DPT among LET patients found that the DPT group has significantly reduced pain both at rest and during motion in the intermediate term (12 weeks). In function improvement, the DPT group had significantly improved QuickDASH scores compared to other treatments at 12 weeks. Nevertheless, there were only insignificant short-term improvements in pain and function in the DPT group. These results appear to be explained by the fact that the mechanism of DPT requires several months for the regenerative process.

Overall, we found that the positive findings were based on underpowered studies with a moderate to high risk of bias, and which thus should be interpreted with a high degree of caution.

We found moderate to high heterogeneity in some outcomes, a result which could be explained by several factors. First, participants included in the studies had subacute to chronic onset of pain, with the mean initial onset occurring between 5.7 and 61.7 months prior to the start of the study. Second, there was a high variation in the injection formula in the DPT group, with the injected volume ranging from 1.5 to 10 ml and the total number of injections varying from 1 to 4. The concentration of DPT, however, was quite consistent, ranging from 15 to 20% dextrose, the amount commonly used in the treatment of tendinopathy.¹² Finally, there were differences in the comparators to DPT, including active and non-active treatments which could have increased the heterogeneity of the results. Unfortunately, we were not able to perform further sensitivity analyses due to the small number of included studies.

Two RCTs of prolotherapy injected solutions that combined dextrose with other sclerosing substances.^{29,30} The authors excluded these two studies in order to determine

the effect of a pure dextrose-containing solution. Finally, only two studies included a comparison of DPT with non-active comparators.^{16,20} Rabago et al.¹⁶ compared the efficacy of DPT to “wait and see”, the natural history of the disease. The findings of that study demonstrated that DPT could improve functional outcomes as assessed with PTREE better than “wait and see” in both the short and intermediate term. PFG of the DPT group was also greater than the “wait and see” group at 12 weeks. Another RCT²⁰ which compared DPT with saline injection showed greater pain reduction in the short and intermediate term in the DPT group. Nevertheless, only insignificant differences in improvement of the affected/unaffected PFG were found between the two groups. Although their findings showed that DPT seemed to be more effective than non-active comparators in reducing pain and providing functional improvement, the authors found these two studies^{16,20} had a rather high risk of bias, making it difficult to draw conclusions.

One of the included RCTs had a low risk of bias and high quality of evidence comparing the efficacy of DPT with physiotherapy.¹⁷ That study reported that physiotherapy demonstrated superior results to DPT in functional outcome as evaluated by PFG and PTREE. That form of treatment is easily accessible in low- and middle-income countries, although physiotherapy has the drawback of requiring multiple out-patient visits.

A previous meta-analysis reported greater results in pain and functional outcomes with PRP injection compared to corticosteroid injection in LET patients.^{2,3} Treatment which focuses on the regenerative process has recently been explored in chronic tendinopathy as well as DPT. The studies of Bayat et al.¹⁹ comparing the efficacy of DPT to corticosteroid injection found significant pain reduction and reduced disability in QuickDASH scores with DPT, although the study had a moderate risk of bias and a high probability of imprecision. Additionally, corticosteroid injection was found to have a detrimental effect at 12 weeks, so the superior efficacy of the DPT compared to the corticosteroid injection should be interpreted cautiously.⁷ However, in one study of overall chronic musculoskeletal pain, there was evidence that DPT had a therapeutic effect comparable to that of corticosteroid and PRP injection.¹⁵ Another study reported that steroid injection leads to a higher rate of surgery, although injection could delay the time to surgery.³¹ Hence, based on the pathophysiology of the disease and the adverse effects related to injection therapy in LET, DPT or the other regenerative therapy can be considered an alternative to corticosteroids.

Hyaluronic acid (HA) has a proven efficacy in pain reduction and functional improvement in osteoarthritis as well as tendinopathy.³²⁻³³ The main mechanism of HA for osteoarthritis is chondroprotection. In tendinopathy, promoting collagen synthesis in the extracellular matrix is the key mechanism.³³ Results from Apaydin et al.²¹ reported greater efficacy of DPT than HA in LET, suggesting consideration should be given to

the use of DPT injection in patients living in low- and middle-income countries.

When compared to radial ESWT, DPT demonstrated significantly lower efficacy in terms of pain reduction and functional improvement in the short term.¹⁸ However, intermediate to long-term effects were not assessed in that study. In practice, a limitation of ESWT in developing countries is the expense of machine maintenance.

Two important points were identified in this present meta-analysis. First, DPT seems to reduce the severity of pain and disability by 12 weeks. Second, DPT is a good option among the injection therapies even though it has demonstrated lower efficacy than physiotherapy and radial ESWT because it can be performed without ultrasound guidance, using palpation to determine the precise anatomical location, and because it maintains a constant dextrose concentration of 15-20%.

There were some limitations in the present study. (1) The authors selected RCTs that used only pure dextrose, leading to a smaller number of studies included for analysis. The authors did not perform subgroup analysis; thus, the cause of the heterogeneity could not be clearly explained. (2) The comparator groups were varied and there were few studies which included a non-active control. (3) The total injected volume and number of injections varied among the included studies. (4) Only one study¹⁷ evaluated long-term outcomes, so the long-term effect of DPT for treating LET patients could not be evaluated. Further high-quality RCTs which compare DPT to a non-active control is required to obtain more explicit results.

Conclusions

More high-quality RCTs of dextrose prolotherapy are needed to determine its benefit for patients with LET. The main reason for the inconclusive results of most of the RCTs reviewed was a moderate to high risk of bias. The only study with a reasonable number of participants and a low risk of bias reported that DPT was significantly inferior to the physiotherapy.

Disclosure

The authors declare that there are no conflicts of interest.

Acknowledgements

The authors would like to express their deep gratitude to Professor Dr. Paweena Susantitaphong, MD., PhD. for enlightening us regarding meta-analysis research.

References

1. Thompson C, Visco C. Lateral epicondylitis: emerging management options. *Curr Sports Med Rep*. 2015;14:215-20.
2. Houck DA, Kraeutler MJ, Thornton LB, McCarty EC, Bravman JT. Treatment of lateral epicondylitis with autologous blood, platelet-rich plasma, or corticosteroid injections: a systematic review of overlapping meta-analyses. *Orthop J Sports Med*. 2019;7.

doi:10.1177/2325967119831052.

3. Xu Q, Chen J, Cheng L. Comparison of platelet rich plasma and corticosteroids in the management of lateral epicondylitis: a meta-analysis of randomized controlled trials. *Int J Surg*. 2019;67:37-46.
4. Keijsers R, de Vos RJ, Kuijer PPF, van den Bekerom MP, van der Woude HJ, Eygendaal D. Tennis elbow. *Shoulder Elbow*. 2019;11:384-92.
5. Chen J, Wang A, Xu J, Zheng M. In chronic lateral epicondylitis, apoptosis and autophagic cell death occur in the extensor carpi radialis brevis tendon. *J Shoulder Elbow Surg*. 2010;19:355-62.
6. Alfredson H, Ljung BO, Thorsen K, Lorentzon R. In vivo investigation of ECRB tendons with microdialysis technique—no signs of inflammation but high amounts of glutamate in tennis elbow. *Acta Orthop Scand*. 2000;71:475-9.
7. Claessen FMAP, Heesters BA, Chan JJ, Kachooei AR, Ring D. A meta-analysis of the effect of corticosteroid injection for enthesopathy of the extensor carpi radialis brevis origin. *J Hand Surg Am*. 2016;41:988-98.e2.
8. Arirachakaran A, Sukthuyat A, Sisayanarane T, Laoratana-voraphong S, Kanchanatawan W, Kongtharvonskul J. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. *J Orthop Traumatol*. 2016;17:101-12.
9. Simental-Mendía M, Vilchez-Cavazos F, Álvarez-Villalobos N, Blázquez-Saldaña J, Peña-Martínez V, Villarreal-Villarreal G, et al. Clinical efficacy of platelet-rich plasma in the treatment of lateral epicondylitis: a systematic review and meta-analysis of randomized placebo-controlled clinical trials. *Clin Rheumatol*. 2020; 39:2255-65.
10. Yao G, Chen J, Duan Y, Chen X. Efficacy of extracorporeal shock wave therapy for lateral epicondylitis: a systematic review and meta-analysis. *Biomed Res Int*. 2020 Mar 18;2020:2064781. doi: 10.1155/2020/2064781.
11. Yan C, Xiong Y, Chen L, Endo Y, Hu L, Liu M, et al. A comparative study of the efficacy of ultrasonics and extracorporeal shock wave in the treatment of tennis elbow: A meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2019;14:248. doi:10.1186/s13018-019-1290-y.
12. Trescot A. Everything old is new again: new developments in prolotherapy. *Tech Reg Anesth Pain Manag*. 2015;19:14-8.
13. Chung MW, Hsu CY, Chung WK, Lin YN. Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth? a systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99(46):e23201. doi: 10.1097/MD.00000000000023201.
14. Sit RW, Chung VCh, Reeves KD, Rabago D, Chan KK, Chan DC, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: a systematic review and meta-analysis. *Sci Rep*. 2016;6:25247. doi:10.1038/srep25247.
15. Bae G, Kim S, Lee S, Lee WY, Lim Y. Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis. *Anesth Pain Med (Seoul)*. 2021;16:81-95.
16. Rabago D, Lee KS, Ryan M, Chourasia AO, Sesto ME, Zgierska A, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylitis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. *Am J Phys Med Rehabil*. 2013;92:587-96.
17. Yelland M, Rabago D, Ryan M, Ng SK, Vithanachchi D, Manickaraj N, et al. Prolotherapy injections and physiotherapy used singly and in combination for lateral epicondylalgia: a single-blinded randomised clinical trial. *BMC Musculoskelet Disord*. 2019;20:509. doi:10.1186/s12891-019-2905-5.
18. Ahadi T, Esmaeili Jamkarani M, Raissi GR, Mansoori K, Emami Razavi SZ, Sajadi S. Prolotherapy vs radial extracorporeal shock wave therapy in the short-term treatment of lateral epicondylitis: a randomized clinical trial. *Pain Med*. 2019;20:1745-1749.
19. Bayat M, Raeissadat SA, Mortazavian Babaki M, Rahimi-Dehghan S. Is dextrose prolotherapy superior to corticosteroid injection in patients with chronic lateral epicondylitis? a randomized clinical trial. *Orthop Res Rev*. 2019;11:167-75.
20. Akcay S, Gurel Kandemir N, Kaya T, Dogan N, Eren M. Dextrose prolotherapy versus normal saline injection for the treatment of lateral epicondylopathy: a randomized controlled trial. *J Altern Complement Med*. 2020;26:1159-68.
21. Apaydin H, Bazancir Z, Altay Z. Injection therapy in patients with lateral epicondylalgia: hyaluronic acid or dextrose prolotherapy? a single-blind, randomized clinical trial. *J Altern Complement Med*. 2020;26:1169-75.
22. Covidence systematic review software [Internet]. Australia: Veritas Health Innovation; 2014. Covidence systematic review; 2014 [cited 2021 Aug 17]; Available from: www.covidence.org
23. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005 Apr 20;5:13. doi: 10.1186/1471-2288-5-13.
24. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014 Dec 19;14:135. doi:10.1186/1471-2288-14-135.
25. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2* [Internet]. [place unknown]: Cochrane; 2021 [updated 2021 February; cited 2021 August 19]. Available from: www.training.cochrane.org/handbook
26. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;366:l4898. doi:10.1136/bmj.l4898.
27. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth*. 2021;12:55-61.
28. Cochrane Consumers And Communication La Trobe University, Ryan R, Hill S. How to GRADE. La Trobe [Internet]. 2018 [cited 2021 Aug 17]; Available from: https://opal.latrobe.edu.au/articles/How_to_GRADE/6818894
29. Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E. The efficacy of prolotherapy for lateral epicondylitis: a pilot study. *Clin J Sport Med*. 2008;18:248-54. doi:10.1097/JSM.0b013e318170fc87.
30. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylitis: a randomized controlled trial. *PM R*. 2011;3:706-15.
31. Kachooei AR, Talaei-Khoei M, Faghfour A, Ring D. Factors associated with operative treatment of enthesopathy of the extensor carpi radialis brevis origin. *J Shoulder Elbow Surg*. 2016;25:666-70.
32. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. a meta-analysis of randomized controlled trials. *J Bone Joint Surg Am*. 2004;86:538-45.
33. Fogli M, Giordan N, Mazzoni G. Efficacy and safety of hyaluronic acid (500-730kDa) ultrasound-guided injections on painful tendinopathies: a prospective, open label, clinical study. *Muscles Ligaments Tendons J*. 2017;7:388-95.