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PII: S0003-9993(22)00240-4
DOI: https://doi.org/10.1016/j.apmr.2022.01.166
Reference: YAPMR 58489

To appear in: *Archives of Physical Medicine and Rehabilitation*

Received date: 28 September 2021
Revised date: 29 January 2022
Accepted date: 31 January 2022

Please cite this article as: Mengting Zhu MSc , David Rabago MD , Vincent Chi-ho Chung PhD , Kenneth Dean Reeves MD , Samuel Yeung-shan Wong MD , Regina Wing-Shan Sit MD , Effects of Hypertonic Dextrose Injection (Prolotherapy) in Lateral Elbow Tendinosis: A Systematic Review and Meta-analysis, *Archives of Physical Medicine and Rehabilitation* (2022), doi: https://doi.org/10.1016/j.apmr.2022.01.166

Running head: Prolotherapy in Lateral Elbow Tendinosis

Effects of Hypertonic Dextrose Injection (Prolotherapy) in Lateral Elbow Tendinosis: A Systematic Review and Meta-analysis

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Abstract

Objective: To systematic review the effectiveness of hypertonic dextrose prolotherapy (DPT) on pain intensity and physical functioning in patients with lateral elbow tendinosis (LET) compared with other active non-surgical treatments.

Data Sources: Systematic search of CENTRAL, MEDLINE, EMBASE, Web of Science, PubMed, Dimensions, Global Health, NHS Health Technology Assessment, AMED and OVID nursing database from inception to 15 June 2021, without language restrictions.

Study Selection: Two reviewers independently identified parallel or cross-over RCTs that evaluated the effectiveness of DPT in LET. The search identified 245 records; data from 8 studies (354 patients) were included.

Data Extraction: Two reviewers independently extracted data and assessed included studies. The Cochrane Risk of Bias 2 tool was used to evaluate risk of bias. The Grading of Recommendation Assessment, Development, and Evaluation approach was used to assess quality of the evidence.

Data Synthesis: Pooled results favored the use of DPT in reducing tennis elbow pain intensity compared with active controls at 12 weeks post-enrollment, with standardized mean difference (SMD) of -0.44 (95% CI -0.88 to -0.01, P =0.04) and of moderate heterogeneity (I^2= 49%). Pooled results also favored the use of DPT on physical functioning compared with active controls at 12 weeks, with DASH score achieving mean difference (MD) -15.04 (95% CI -20.25

to -9.82, P < 0.001) and of low heterogeneity (I^2= 0.0%). No major related adverse events have been reported.

Conclusions: DPT is superior to active controls at 12 weeks for decreasing pain intensity and functioning by margins that meet criteria for clinical relevance in the treatment of LET. While existing studies are too small to assess rare adverse events, for LET patients, especially those refractory to first-line treatments, DPT can be considered a non-surgical treatment option in carefully selected patients. Further high-quality trials with comparison with other injection therapies are needed.

Keywords: prolotherapy**,** hypertonic dextrose injection; lateral elbow tendinosis; meta-analysis; pain; physical functioning.

Registration: PROSPERO registry (CRD42021265178)

List of abbreviations:

AMED	Allied and Complementary Medicine
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence intervals
DASH	Disabilities of the Arm, Shoulder and Hand
DPT	Hypertonic dextrose prolotherapy
GRADE	Grading of Recommendation Assessment, Development, and Evaluation
I^2	I square
LET	lateral elbow tendinosis
MCID	minimal clinically important difference

MD	mean difference
NRS	numerical rating scale
PRP	platelet-rich plasma
PTREE	Patient-Related Tennis Elbow Evaluation
RCT	randomized controlled trial
SMD	standardized mean difference
TRPV 1	transient receptor potential vanilloid type 1
VAS	visual analog scale
WMD	weighted mean difference

Introduction

Lateral elbow tendinosis (LET), also known as tennis elbow, lateral epicondylitis, or lateral epicondylalgia, has a significant disease burden of 2.5 to 3.5 per 1000.[1] It is most commonly seen in the middle-aged population,[2] with a higher prevalence among industrial workers[3] and amateur tennis players.[4] Although most cases are self-limiting with symptoms resolving in 12 months, up to 20% are refractory to conservative care,[5] with considerable individual morbidity, substantial healthcare resource utilization, and lost time from work.[6]

Exercise-based rehabilitation, such as eccentric, isometric, and concentric loading exercises, are the primary LET treatment.[7] However, a recent review has shown that the magnitude of the effect is small compared with other passive interventions.[8] Other second-line interventions such as corticosteroid injections,[9] shock wave therapy,[10] laser therapy,[11] bracing,[12] and newer options

such as platelet-rich plasma,[13] and autologous whole blood injection,[14] have been evaluated in many randomized trials but there is no definitive evidence or consensus on which should be considered as the priority in LET.[15, 16]

Hypertonic dextrose prolotherapy (DPT) is an injection therapy used to treat chronic painful musculoskeletal conditions.[17, 18] The historical understanding posits that DPT facilitates healing and subsequent pain control by initiating a temporary inflammatory reaction with related tissue proliferation.[19-22] Recent literature also suggests possible direct sensorineural effects of DPT on neuralgic pain.[23] The role of DPT in LET has been evaluated in a growing number of methodologically higher quality clinical trials, which reported beneficial effects on pain and function using standardized outcomes;[24-26] yet, the findings have not been synthesized. In a recent meta-analysis, a conclusion that injection therapy did not improve pain and functional outcomes but increased risk of adverse events in LET has been made without including DPT in the analysis.[27] Therefore, we conducted this systematic review of randomized control trials (RCTs) to assess and analyze the effectiveness of DPT in LET.

Methods

Study design

We followed the statement on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for RCTs.[28] The protocol has been registered in the PROSPERO registry (CRD42021265178).

Eligibility Criteria

This review included parallel or cross-over randomized controlled trials (RCTs) that evaluated the efficacy or effectiveness of DPT in LET regardless of blinding.[29] For cross-over RCTs, only data before the cross-over period was used.[30]

Information sources

Potential studies were identified by searching electronic databases, including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science, PubMed, Dimensions, Global Health, NHS Health Technology Assessment, Allied and Complementary Medicine (AMED), and OVID nursing database. A systematic search of all databases was conducted from their inception to 15 June 2021, with no language limitations. Reference lists of relevant studies were also screened for additional possible studies.

Search strategy

The strategy had two components including terms for DPT and LET. Keywords for population were: "Tennis Elbow"[MeSH] OR "Elbow Tendinopathy"[MeSH] OR lateral epicondyle*[all fields] OR lateral humeral epicondylitis*[all fields]; and keywords for intervention were: "Prolotherapy"[MeSH] OR dextrose [all fields] OR prolotherapy [all fields]. Search keys were summarized in appendix 1.

Types of participants

This study included participants with a diagnosis of LET, defined as pain over the lateral humeral epicondyle provoked by palpation and resisted wrist/middle finger extension or

gripping, and with or without confirmatory hypoechoic lesions on ultrasonography.[31]

Types of interventions

For inclusion, DPT had to be administered to at least one group within the trial. Co-interventions were allowed as long as they were uniform across all groups such that the effects of DPT could be isolated; for example, studies comparing DPT plus dry needling with dry needling alone would be included, however studies comparing DPT plus dry needling with DPT alone would not be included.

Types of comparison controls

Comparison groups were classified into active and inactive controls according.[32] For inactive control, we defined as "no treatment", "standard care", or a "waiting list control", and these included watchful-waiting, bracing and usual care. For active control, we defined as the use of different injection solutions or a different kind of therapy, which included exercise,[8] manual therapy,[33] dry needling,[34] shock-wave,[10] laser,[11] injections of corticosteroids,[9] platelet rich plasma injection,[13] autologous whole blood injection,[14] and normal saline.[35]

Outcome measures

The primary outcome of interest was pain reduction in LET, measured by visual analogue scale (VAS 0-100mm), numerical rating scale (NRS 0-10), or algometry. Secondary outcomes included handgrip strength in kilogram (kg)[36], Patient-Related Tennis Elbow Evaluation (PRTEE) score and its subscales,[37] and Disabilities of the Arm, Shoulder and Hand (DASH).[38]

Study selection and data extraction

All potential studies from the search process were imported into the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Two reviewers (MTZ, RWSS) independently screened electronically retrieved titles and abstracts for potentially eligible trials and evaluated potential relevant full texts and determined study eligibility. For eligible studies, data were extracted independently by MTZ and RWSS using a data extraction form. The extracted information included authors, publication year, follow-up duration, number of participants and their characteristics, features of interventions and controls, treatment outcomes. Discrepancies in study selection and data extraction were resolved by a third reviewer (DR).

Risk of bias assessment

The Cochrane Risk of Bias 2 (RoB 2) tool was used to evaluate the following five RoB domains: bias arising from randomization process; deviation from intended interventions; missing outcome data; measurement of outcome and selection of the reported results.[39] The RoB was assessed independently by two reviewers (MTZ, RWWS); any discrepancy was resolved by a third reviewer (VCHC).

Quality of evidence

The Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of the evidence across studies for pain intensity, DASH and PTREE cumulative score, and grip strength separately. Evidence were downgraded 1 place if (1) risk of bias was evident (majority of trials were at moderate or high risk of bias), (2) there

was evidence of unexplained inconsistency (I^2>50%), (3) there was evidence of indirectness in population or outcome, (4) there was evidence of imprecision (wide 95% CI >0.8 for SMD and > MCID for MD), or (5) there was publication bias (visual inspection of funnel plots when there were at least 10 trials in the meta-analysis); When there was less than 10 trials, evidence consists of a small number of studies (≤ 2) with a small number of participants (≤ 100). The quality of evidence was classified into 4 categories: very low, low, moderate, and high.

Statistical Analysis

All meta-analyses were conducted using Review Manager (RevMan version 5.4) software.[40] Pairwise meta-analysis was performed using a random-effects model, taking into account possible variations in effect sizes across trials.[41] For continuous outcomes measured using different scales, data was summarized as standardized mean differences (SMD), with 95% confidence intervals (CI). The magnitude of the SMD was determined using the standard approach: small, SMD = 0.2; medium, SMD = 0.5; and large, SMD = 0.8.[42] Weighted mean difference (WMD) was used to measure outcomes sharing the same unit of measure, and its potential clinical significance was interpreted based on the minimal clinical important difference (MCID). The MCID for pain intensity was 1.65 on the 11-point NRS and 16.55 on 100-mm VAS,[43] the MCID for PRTEE cumulative score among participants with LET was 7/100 or 22% of baseline PRTEE score[44], the MCID for grip strength was 17 kg for patients with LET,[45] and the MCID for the DASH cumulative score was 10.83 points.[38] I square (I^2) statistic was calculated to quantify the degree of heterogeneity across studies. An I^2 level of less than <25%, 25-50%, and greater than 50% indicates low, moderate, or high heterogeneity, respectively.[46] Funnel plots were constructed, where possible, to explore publication bias.

Results

Eligible studies

The search strategy retrieved 245 citations from all databases after excluding 99 duplicates. After screening based on the titles and abstracts, we retrieved 27 full texts for further assessment. Of these, 19 were excluded for the following reasons: no eligible data (n=6), duplicate (n=5), a narrative review (n=4), trial registration only (n=2), not an RCT (n=1) and conference abstract only (n=1). Finally, eight full texts met the inclusion criteria and were included for descriptive synthesis,[24-26, 47-51] among which five were included in the quantitative synthesis procedure.[24-26, 50, 51] **(Figure 1)** Among the three that were not included in the quantitative synthesis, one study had no available data for extraction at 12-16 weeks,[52] and two studies had complex intervention components in addition toDPT.[48, 50] There were no discrepancies in study selection and data extraction.

Characteristics of included trials

Detailed descriptions of the characteristics of the eight included studies were summarized in **Table 1**. Study sample sizes ranged from 24 to 120, with a total of 354 individuals. The study period ranged from 8 weeks to 52 weeks post-enrollment. The injection frequency ranged from a single injection to four injections, weekly to four weeks apart, with dextrose concentration varying from 12.5% to 50%.

Risk of Bias Assessment

Overall, 87.5% (7/8) of outcomes were scored as having “some concerns”, and 12.5% (1/8) of outcomes were rated as having high risk of bias (**Figure 2**). In the domain of “bias arising from

randomization process," 1 study had low bias,[48] and 7 had some bias.[24-26, 47, 49-51] In the domain of "bias due to deviations from intended interventions, 7 studies had low bias,[24-26, 47, 49-51] 1 had some bias.[48] In the domain of "bias due to missing outcome data," all 8 studies had low bias.[24-26, 47-51] In the domain of "bias in measurement of outcome," 7 had low bias,[24-26, 47-49, 51] and 1 study had high bias.[50] In the domain "bias in selection of reported outcome", 7 had some bias,[24, 26, 47-51] and 1 had low bias.[25] Details of response options for signaling questions in 5 domains and overall domain were summarized in **appendix 2**.

DPT versus active controls on tennis elbow pain intensity at 12 weeks

In this comparison, four RCTs (n=183) were eligible for pooling.[24-26, 51] Visual Analog Scale (VAS), numerical rating scale (NRS) were reported, with SMDs calculated in the random effect meta-analyses. Pooled results favored the use of DPT in reducing tennis elbow pain intensity compared with active control, with SMD -0.44 (95% CI -0.88 to -0.01, P =0.04) and of moderate heterogeneity (I^2= 49%). **(Figure 3a**)

DPT versus active controls on DASH cumulative score at 12 weeks

In this comparison, three RCTs (n=110) were eligible for pooling. Pooled results favored the use of DPT compared with active control, with MD -15.04 (95% CI -20.25 to -9.82, P < 0.001) and of low heterogeneity (I^2= 0%). **(Figure 3b)**

DPT versus active controls on PRTEE cumulative score at 12 weeks

In this comparison, two RCTs (n=123) were eligible for pooling.[24, 51] The same scale PRTEE were reported, with MDs calculated in the random effect meta-analyses. Pooled results suggested

no significant effect of DPT on improving PRTEE score, with MD 2.35 (95% CI -9.81 to 14.51, P =0.70), and of moderate heterogeneity (I^2= 42%). **(Figure 3c)**

DPT versus active controls on grip strength at 12-16 weeks

Two RCTs (n=105) were eligible for pooling; a dynamometer was used in one trial to assess grip strength, while another trial did not describe the measurement method.[25, 51] Pooled results suggested no significant effect of DPT on improving grip strength, with SMD -0.06 (95% CI -1.00 to 0.88, P =0.90), and of high heterogeneity (I^2= 80%). **(Figure 3d)**

Adverse events:

Injection side effects were reported in 7 of the 8 included trials. One trial reported a DPT participant developed neuropraxia of the posterior interosseous nerve after the 4th treatment, but symptoms resolved in 3 months and there was no further negative impact; another DPT participant developed painful bruising over the forearm after the 2nd treatment which resolved in two weeks.[51] Two trials reported mild to moderate self-limiting post-injection pain.[48, 49] The other 4 trials reported no adverse events in the DPT group throughout the study period.[24, 26, 47, 50] Adverse events were not reported in one study.[25] Overall, there were no significant related adverse events of DPT in the included trials.

Quality of evidence with GRADE approach

The overall quality of evidence presented in this review ranges from very low to moderate based the assessment with the GRADE approach **(appendix 3**). The assessment showed low certainty for DPT compared with active controls in reducing pain intensity, moderate certainty in

improving DASH cumulative score. The assessment showed very low to low certainty on PRTEE cumulative score and grip strength.

Discussion

This study showed that DPT is superior to other active controls in reducing elbow pain, with a small to medium effect size and moderate heterogeneity at 12 weeks post-enrollment, with evidence from low to moderate quality studies. We also found that DPT improved the DASH score by 15.04 points, exceeding the MCID of 10.83 points for this measure in LET.[38] No statistically significant improvement was reported in PRTEE score and grip strength. Statistical comparison with inactive controls was not possible as only one trial used waitlist as the control group.[49]

Comparing to the standard treatment of LET, DPT achieved a larger effect size than corticosteroid injection, which has demonstrated a statistically significant SMD of 0.38 in reducing pain intensity in LET at around 12 weeks.[53] However, the effect size of DPT is smaller than eccentric strengthening exercise, which has a statistically significant SMD of 1.12 in pain reduction.[54] Platelet-rich plasma (PRP) is a recommended injection therapy for LET and has been shown to be more effective than corticosteroids over time.[55] However, no RCT has been conducted comparing DPT and PRP in LET. Therefore, we suggest that DPT can be considered as an adjunctive therapy to exercise, and an alternative injection therapy to corticosteroids in LET. Its effectiveness as compared to platelet rich plasma needs to be confirmed in future trials.

The mechanism of DPT in decreasing musculoskeletal pain, including LET pain and other soft tissue conditions, is likely due to its tissue proliferation and sensorineural analgesic effects. In-vitro study has shown that exposure of tenocytes to DPT elicited an inflammatory response through the up-regulation of pro-inflammatory markers including interleukin-8, cyclooxygenase-2, and prostaglandins-2, and downregulation of anti-inflammatory marker growth factor-beta. This suggested the possible mechanism of DPT on initiating the wound-healing cascades.[56] A rodent study of medial collateral ligaments injected with dextrose reported a statistically significant increased cross-sectional area of dextrose-injected medial collateral ligaments by 30% and 90% compared with saline and uninjured controls.[20] In a rabbit model, injection of DPT into the connective tissue in the carpal tunnel produced thickening of the collagen bundles and increase energy absorption when compared with saline controls.[21, 22] Dextrose solution hyperpolarises nerves by opening their potassium channels, thereby decreasing signal transmission in nociceptive pain fibres.[57] In addition, glucose solutions may work by blocking transient receptor potential vanilloid type 1 (TRPV 1), thus reduce the action potentials and the release of substance P and calcitonin gene-related peptide, which theoretically could minimise neuropathic pain.[58, 59]

Strengths of the current study include timely conduct of a study to review an area that is rapidly emerging, clinically important, and has disparate findings. We used a rigorous methodology that conformed to best practice guidelines.

Study limitations

There were several limitations of the current study. The number of included studies and total participant sample size were small, and quantitative syntheses included a small number of studies in most comparisons. For the same reason, we were unable to generate funnel plots to assess publication bias.[60] The time frame of 12 to 16 weeks available for data pooling was short; thus, longer term effects remain uncertain. There was high heterogeneity across trials; this could be partially explained by variation in the number, frequency, volume and concentrations of dextrose solutions used, and the nature of different active controls.

Conclusions

In conclusion, our systematic review and meta-analysis found that DPT outperformed active controls for improving pain intensity and function which met criteria for clinical relevance in the treatment of LET. Hence, for patients with LET, especially those who are refractory to exercise therapy, DPT can be considered as an appropriate non-surgical treatment option. Further high-quality trials with longer-term follow-up, adequate sample size and direct comparison with other injection therapies are needed. Future research of the mechanism of action will further inform the assessment of DPT in LET.

References

1. Sanders TL, Jr., Maradit Kremers H, Bryan AJ, Ransom JE, Smith J, Morrey BF. The epidemiology and health care burden of tennis elbow: a population-based study. Am J Sports Med 2015;43(5):1066-71.

2. Shiri R, Viikari-Juntura E, Varonen H, Heliövaara M. Prevalence and determinants of

lateral and medial epicondylitis: a population study. American journal of epidemiology 2006;164(11):1065-74.

3. Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Occupation and epicondylitis: a population-based study. Rheumatology 2012;51(2):305-10.

4. Kitai E, Itay S, Ruder A, Engel J, Modan M. An epidemiological study of lateral epicondylitis (tennis elbow) in amateur male players. Proceedings of the Annales de Chirurgie de la Main: Elsevier; 1986.

5. Buchbinder R, Green SE, Struijs PA. Tennis elbow. BMJ clinical evidence 2008;2008.

6. Sanders TL, Maradit Kremers H, Bryan AJ, Ransom JE, Morrey BF. Health care utilization and direct medical costs of tennis elbow: a population-based study. Sports health 2016;8(4):355-8.

7. Bisset LM, Vicenzino B. Physiotherapy management of lateral epicondylalgia. Journal of physiotherapy 2015;61(4):174-81.

8. Karanasios S, Korakakis V, Whiteley R, Vasilogeorgis I, Woodbridge S, Gioftsos G. Exercise interventions in lateral elbow tendinopathy have better outcomes than passive interventions, but the effects are small: a systematic review and meta-analysis of 2123 subjects in 30 trials. British journal of sports medicine 2021;55(9):477-85.

9. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet (London, England) 2010;376(9754):1751-67.

10. Xiong Y, Xue H, Zhou W, Sun Y, Liu Y, Wu Q et al. Shock-wave therapy versus corticosteroid injection on lateral epicondylitis: a meta-analysis of randomized controlled trials. The Physician and sportsmedicine 2019;47(3):284-9.

11. Dingemanse R, Randsdorp M, Koes BW, Huisstede BM. Evidence for the effectiveness of electrophysical modalities for treatment of medial and lateral epicondylitis: a systematic review. British journal of sports medicine 2014;48(12):957-65.

12. Kroslak M, Pirapakaran K, Murrell GA. Counterforce bracing of lateral epicondylitis: a prospective, randomized, double-blinded, placebo-controlled clinical trial. Journal of shoulder and elbow surgery 2019;28(2):288-95.

13. 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. Clinical rheumatology 2020;39(8):2255-65.

14. Tsikopoulos K, Tsikopoulos A, Natsis K. Autologous whole blood or corticosteroid injections for the treatment of epicondylopathy and plantar fasciopathy? A systematic review and meta-analysis of randomized controlled trials. Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine 2016;22:114-22.

15. Sims SEG, Miller K, Elfar JC, Hammert WC. Non-surgical treatment of lateral epicondylitis: a systematic review of randomized controlled trials. Hand (New York, NY) 2014;9(4):419-46.

16. Niedermeier SR, Crouser N, Speeckaert A, Goyal KS. A Survey of Fellowship-Trained Upper Extremity Surgeons on Treatment of Lateral Epicondylitis. HAND 2018;14(5):597-601.

17. Rabago D, Nourani B. Prolotherapy for osteoarthritis and tendinopathy: a descriptive review. Current rheumatology reports 2017;19(6):34.

18. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Clinical medicine insights: Arthritis and

musculoskeletal disorders 2016;9:CMAMD. S39160.

19. Jensen K, Rabago D, Best TM, Patterson JJ, Vanderby R. Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res 2008;26:816-23.

20. Jensen KT, Rabago D, Best TM, Patterson JJ, Vanderby R. Longer term response of knee ligaments to prolotherapy in a rat injury model. Am J Sports Med 2008;36:1347-57.

21. Yoshii Y, Zhao C, Schmelzer JD, Low PA, An K-N, Amadio PC. The effects of hypertonic dextrose injection on connective tissue and nerve conduction through the rabbit carpal tunnel. Archives of physical medicine and rehabilitation 2009;90(2):333-9.

22. Yoshii Y, Zhao C, Schmelzer JD, Low PA, An K-N, Amadio PC. Effects of multiple injections of hypertonic dextrose in the rabbit carpal tunnel: a potential model of carpal tunnel syndrome development. Hand 2014;9(1):52-7.

23. Wu YT, Ho TY, Chou YC, Ke MJ, Li TY, Tsai CK et al. Six-month Efficacy of Perineural Dextrose for Carpal Tunnel Syndrome: A Prospective, Randomized, Double-Blind, Controlled Trial. Mayo Clinic proceedings 2017;92(8):1179-89.

24. 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. The Journal of Alternative and Complementary Medicine 2020;26(12):1159-68.

25. Apaydin H, Bazancir Z, Altay Z. Injection therapy in patients with lateral epicondylalgia: hyaluronic acid or dextrose prolotherapy? A single-blind, randomized clinical trial. The Journal of Alternative and Complementary Medicine 2020;26(12):1169-75.

26. Bayat M, Raeissadat SA, Babaki MM, Rahimi-Dehgolan S. Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial. Orthopedic research and reviews 2019;11:167.

27. Kim YJ, Wood SM, Yoon AP, Howard JC, Yang LY, Chung KC. Efficacy of Nonoperative Treatments for Lateral Epicondylitis: A Systematic Review and Meta-Analysis. Plastic and Reconstructive Surgery 2021;147(1).

28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336-41.

29. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

30. Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Deutsches Ärzteblatt International 2012;109(15):276.

31. Speers CJ, Bhogal GS, Collins R. Lateral elbow tendinosis: a review of diagnosis and management in general practice. The British journal of general practice : the journal of the Royal College of General Practitioners 2018;68(676):548-9.

32. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.

33. Hoogvliet P, Randsdorp MS, Dingemanse R, Koes BW, Huisstede BM. Does effectiveness of exercise therapy and mobilisation techniques offer guidance for the treatment of lateral and medial epicondylitis? A systematic review. British journal of sports medicine 2013;47(17):1112-9.

34. Navarro-Santana MJ, Sanchez-Infante J, Gómez-Chiguano GF, Cleland JA, López-de-Uralde-Villanueva I, Fernández-de-Las-Peñas C et al. Effects of trigger point dry needling on lateral epicondylalgia of musculoskeletal origin: a systematic review and meta-analysis. Clinical

rehabilitation 2020;34(11):1327-40.

35. Gao B, Dwivedi S, DeFroda S, Bokshan S, Ready LV, Cole BJ et al. The Therapeutic Benefits of Saline Solution Injection for Lateral Epicondylitis: A Meta-analysis of Randomized Controlled Trials Comparing Saline Injections With Nonsurgical Injection Therapies. Arthroscopy 2019;35(6):1847-59.e12.

36. Stratford PW, Norman GR, McIntosh JM. Generalizability of grip strength measurements in patients with tennis elbow. Physical therapy 1989;69(4):276-81.

37. Macdermid J. Update: The Patient-rated Forearm Evaluation Questionnaire is now the Patient-rated Tennis Elbow Evaluation. Journal of hand therapy : official journal of the American Society of Hand Therapists 2005;18(4):407-10.

38. Franchignoni F, Vercelli S, Giordano A, Sartorio F, Bravini E, Ferriero G. Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (QuickDASH). The Journal of orthopaedic and sports physical therapy 2014;44(1):30-9.

39. Sterne JA, 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;366.

40. Keijsers R, Kuijer PPFM, Koenraadt KLM, van den Bekerom MPJ, Gerritsma-Bleeker CLE, Beumer A et al. Effectiveness of standardized ultrasound guided percutaneous treatment of lateral epicondylitis with application of autologous blood, dextrose or perforation only on pain: a study protocol for a multi-center, blinded, randomized controlled trial with a 1 year follow up. BMC musculoskeletal disorders 2019;20(1):351.

41. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research synthesis methods 2010;1(2):97-111.

42. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 2013.

43. Bahreini M, Safaie A, Mirfazaelian H, Jalili M. How much change in pain score does really matter to patients? The American journal of emergency medicine 2020;38(8):1641-6.

44. Poltawski L, Watson T. Measuring clinically important change with the Patient-rated Tennis Elbow Evaluation. Hand Therapy 2011;16:52-7.

45. Bobos P, Nazari G, Lu Z, MacDermid JC. Measurement Properties of the Hand Grip Strength Assessment: A Systematic Review With Meta-analysis. Arch Phys Med Rehabil 2020;101(3):553-65.

46. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327(7414):557-60.

47. Ahadi T, Jamkarani ME, Raissi GR, Mansoori K, Razavi SZE, Sajadi S. Prolotherapy vs Radial Extracorporeal Shock Wave Therapy in the Short-term Treatment of Lateral Epicondylosis: A Randomized Clinical Trial. Pain Medicine 2019;20(12):2612-.

48. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. PM & R : the journal of injury, function, and rehabilitation 2011;3(8):706-15.

49. Rabago D, Lee KS, Ryan M, Chourasia AO, Sesto ME, Zgierska A et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. American journal of physical medicine & rehabilitation 2013;92(7):587-96.

50. Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine 2008;18(3):248-54.

51. Yelland M, Rabago D, Ryan M, Ng S-K, 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 musculoskeletal disorders 2019;20(1):509.

52. 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 Epicondylosis: A Randomized Clinical Trial. Pain Med 2019;20(9):1745-9.

53. Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomised controlled trials. Annals of the Rheumatic Diseases 2009;68(12):1843-9.

54. Chen Z, Baker NA. Effectiveness of eccentric strengthening in the treatment of lateral elbow tendinopathy: A systematic review with meta-analysis. Journal of Hand Therapy 2021;34(1):18-28.

55. Huang K, Giddins G, Wu LD. Platelet-Rich Plasma Versus Corticosteroid Injections in the Management of Elbow Epicondylitis and Plantar Fasciitis: An Updated Systematic Review and Meta-analysis. Am J Sports Med 2020;48(10):2572-85.

56. Ekwueme EC, Mohiuddin M, Yarborough JA, Brolinson PG, Docheva D, Fernandes HA et al. Prolotherapy induces an inflammatory response in human tenocytes in vitro. Clinical Orthopaedics and Related Research® 2017;475(8):2117-27.

57. Burdakov D, Jensen LT, Alexopoulos H, Williams RH, Fearon IM, O'Kelly I et al. Tandem-pore K+ channels mediate inhibition of orexin neurons by glucose. Neuron 2006;50(5):711-22.

58. Veronesi B, Oortgiesen M. Neurogenic inflammation and particulate matter (PM) air

pollutants. Neurotoxicology 2001;22(6):795-810.

59. Lyftogt J. Subcutaneous prolotherapy treatment of refractory knee, shoulder, and lateral elbow pain. Australasian Musculoskeletal Medicine 2007;12(2):110.

60. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj 2011;343.

Figure legends

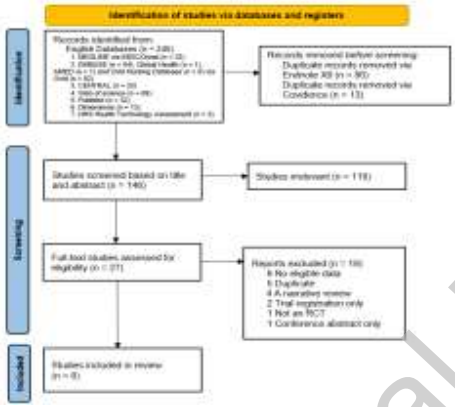

Figure 1. Flowchart of studies selected according to PRISMA (preferred reporting items for systematic reviews and meta-analyses).

Figure 2. Quality assessment of included studies.

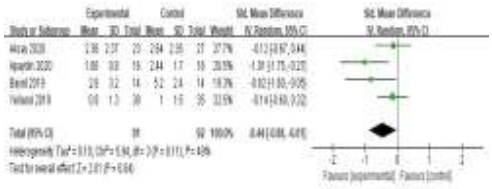

Figure 3a. Dextrose versus active controls on pain intensity (including VAS and NRS score) at 12 weeks

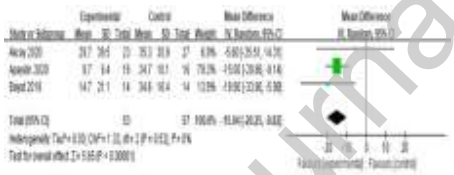

Figure 3b. Dextrose versus active controls on DASH cumulative score at 12 weeks

Figure 3c. Dextrose versus active controls on PRTEE cumulative score at 12 weeks

Figure 3d. Dextrose versus active controls on grip strength via dynamometer at 12-16 weeks

Table 1. Characteristics of the eight included studies.

	Title	Year	Sample size	Sample analysed	Intervention group	Control group(s)	Mean age (SD)	Female (%)	Injection site(s)	Dextrose vol/inj.(ml)	Injection Frequency	Outcomes	Assessment time point	Duration
1	Prolotherapy vs Radial Extracorporeal Shock Wave Therapy in the Short-term Treatment of Lateral Epicondylosis: A Randomized Clinical Trial	Ahadi 2019	33	30	Gp A (n=15): 20% dextrose	Gp B (n=15): shock wave therapy weekly (once weekly for 3 weeks)	46.94 (8.3)	69.60 %	maximal tenderness point	3	Single inj.	VAS pain severity (0–10) grip strength Quick DASH PPT	0, 4, 8 weeks	8 weeks
2	Dextrose Prolotherapy Versus Norma	Akcay 2020	60	50	Gp A (n=23): 15% dextrose	Gp B (n=27): 1.5cc Saline (0.9% NaCl)	Gp A: 48.1 (8	74.00 %	lateral epicondyle, annular ligame	1.5	0, 4, 8 weeks	VAS pain intensity	0, 4, 8, 12 weeks	12 weeks

	l Saline Injection for the Treatment of Lateral Epicondylopathy: A Randomized Controlled Trial						.9) Gp B: 46.7 (8.3)		nt, and supracondylar ridge			(0-10 cm) PRTEE DASH (0-100) pain-free handgrip strength		
3	Injection Therapy in Patients with Lateral Epicondylalgia: Hyaluronic Acid or Dextrose Prolotherapy? A Single-Blind, Randomized Clinical Trial	Apaydin 2020	32	32	Gp A (n=16): 15% dextrose	Gp B (n=16): 30 mg/2 ml 1500 kDa high molecular weight hyaluronic acid	44.5 (1.1)	81.25 %	Gp A: the tenderest point of the lateral epicondyle, the annular ligament, lateral collateral ligament, and tender areas of the extensor tendon. Gp B: the most	5	Gp A: 0, 3, 6 weeks Gp B: 0 week	VAS (0-10cm) Q-DASH (0-100) Pain-free grip strength	0, 6, 12 weeks	12 weeks

									sensitive point in the lateral epicondyle					
4	Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial	Bayat 2019	30	28	Gp A (n=14) : 16% dextrose (containing 2.5 mL dextrose 20% and 1 mL lidocaine 2%)	Gp B (n=14):corticosteroid (1 mL 40 mg/mL methylprednisolone and 2 mL 1% lidocaine)	Gp A: 46.2 (6.4) Gp B: 50.7 (7.5)	60.71 %	The point of maximal tenderness	3	Single inj.	VAS (0-10) Quick DASH (0-100)	0, 4, 12 weeks	12 weeks
5	Prolotherapy Versus Corticosteroid Injections for the Treatment of Lateral Epicondylosis: A Randomized Controlled Trial	Carayannopoulos 2011	24	17	Gp A (n=8): 1.0 mL of procaine, 0.9 mL of P2G (phenol 1.2%, glycerine 12.5 %, and	Gp B (n=9): 1.0 mL of procaine and 1.0 mL of DepoMedrol	Total: 46 (range 35-57) Gp A: 49 (56.2) Gp	64.71 %	Lateral epicondyle of the humerus (LE) (first to the radial side of the annular ligament at the margin between the radial	2	0, 4 weeks	VAS (0-10cm) QVAS DASH (0-100) Painfree and maximum	0, 4, 12, 24 weeks	24 weeks

					dextrose 12.5 % in sterile water) plus 0.1 ml sodium morrhuate		B: 46 (5.3)		head and the ulna) (second to the attachment of the common extensor tendon at the lateral epicondyle) (third to the radial collateral ligament at the tubercle of the radius)			grip strength		
6	Hypertonic Dextrose and Morrhuate Sodium Injections (Prolotherapy) for Lateral Epicondylosis (Tennis Elbow) Result	Rabago 2013	31	27	Gp A (n=8): 20 %Dextrose (4 ml of 50% dextrose + 4 ml of 0.9% saline + 2 ml of 1% lidocaine) Gp B	Gp C (n=10): waitlist	48.2 (7.8)	35.00 %	lateral epicondyle the bone along a short segment of the tendon and the annular ligament at the areas of palpate	10	1, 4, 8 weeks	PRTEE (0-100) pain-free grip strength	0, 4, 8, 16, 32 weeks	32 weeks

	s of a Single-blind, Pilot-Level, Randomized Controlled Trial				(n=9): 10% Dextrose and morrhuate (1 ml of 5% morrhuate sodium + 1.5 ml of 50% dextrose + 2 ml of 1% lidocaine + 2.5 ml of 0.9% saline)				d tenderness and US-documented pathology					
7	The efficacy of prolotherapy for lateral epicondylosis: A pilot study	Scarpone 2008	24	20	Gp A (n=10): 10.7% dextrose (solution consisting of 50% dextrose, 5% sodium morrhuate and 4% lidoc	Gp B (n=10): 0.9% saline	45.7 (10.7)	50.00%	supracondylar ridge lateral epicondyle annular ligament	0.5	3 inj.; 0, 4, 8 weeks	NRS resting elbow pain (0–10 Likert scale) resting grip strength isomet	0, 8, 16, 52 weeks	52 weeks

					aine and 0.5% sens orcai ne. The Stud y phar maci st mixe d the follo wing 35m L steril e solut ion: 7.5m L 50% dextr ose, 5mL of 5% sodiu m morr huate , 2.5m L 4% lidoc aine, 2.5m L 0.5% sens orcai ne and 17.5 mL norm al salin e. The							ric resi stan ce stre ngt h		

					solution is 10.7 % Dextrose and contains 14.7 % sodium morrhuate by volume)									
8	Prolotherapy injections and physiotherapy used singly and in combination for lateral epicondylalgia: a single-blinded randomised clinical trial	Yelland 2019	120	102	Gp A (n=35) 20 % dextrose 20% glucose + 0.4% lignocaine	Gp B (n=34) Physiotherapy Gp C (n=33) combined treatment (prolotherapy+physiotherapy)	49.3 (7.8)	43.33 %	Tenderness points in lateral epicondylalgia, i.e., over the lateral epicondyle, supracondylar ridge, radial head, lateral collateral and annular ligaments, and the common extensor tendon and musculotendi	0.5 to 1.0	4 inj.; 4-weeks apart (0,4,8,12 weeks)	PRTEE GIC NRS pain severity at rest (0-10) NRS the worst pain severity (0-10) pain-free grip strengt	0, 6, 12, 26, 52 weeks	52 weeks

									nous junctio n.			h EQ-5D-3 L		

Abbreviations DASH: Disabilities of the Arm, Shoulder, and Hand; EQ-5D-3L: EuroQol- 5 Dimension 3-level version; GIC: Global impression of change; Gp: group; Inj.: injection; NRS: Numerical Rating Scale; PPT: Pressure Pain Threshold; PRTEE: Patient Rated Tennis Elbow Evaluation; Q-DASH: Quick-Disabilities of the Arm, Shoulder, and Hand; Quick DASH: Disabilities of the Arm, Shoulder, and Hand quick questionnaire; QVAS: Quadruple Visual Analog Scale; VAS: Visual Analog Scale.