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REVIEW ARTICLE (META-ANALYSIS)

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

Mengting Zhu, MSc,[a] David Rabago, MD,[b] Vincent Chi-ho Chung, PhD,[a] Kenneth Dean Reeves, MD,[c] Samuel Yeung-Shan Wong, MD,[a] Regina Wing-Shan Sit, MD[a]

From the [a]The Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Sha Tin, New Territories, Hong Kong, China; [b]Department of Family and Community Medicine, Pennsylvania State University, Hershey, PA; and [c]Private Practice, Roeland Park, KS.

Abstract

Objective: To systematically 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 Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Web of Science, PubMed, Dimensions, Global Health, NHS Health Technology Assessment, Allied and Complementary Medicine, and OVID nursing database from inception to June 15, 2021, without language restrictions.

Study Selection: Two reviewers independently identified parallel or crossover randomized controlled trials 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 postenrollment, with a standardized mean difference of −0.44 (95% confidence interval, −0.88 to −0.01, P=.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 Disabilities of the Arm, Shoulder and Hand scores achieving a mean difference of −15.04 (95% confidence interval, −20.25 to −9.82, P<.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. Although existing studies are too small to assess rare adverse events, for patients with LET, especially those refractory to first-line treatments, DPT can be considered a nonsurgical treatment option in carefully selected patients. Further high-quality trials with comparison with other injection therapies are needed.

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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 health care 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

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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 was made without including DPT in the analysis.[27] Therefore, we conducted this systematic review of randomized controlled 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 crossover RCTs that evaluated the efficacy or effectiveness of DPT in LET regardless of blinding.[29] For crossover RCTs, only data before the crossover period were used.[30]

Information sources

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

List of abbreviations:

CI	**confidence interval**
DASH	**Disabilities of the Arm, Shoulder and Hand**
DPT	**hypertonic dextrose prolotherapy**
GRADE	**Grading of Recommendation Assessment, Development, and Evaluation**
LET	**lateral elbow tendinosis**
MCID	**minimal clinically important difference**
MD	**mean difference**
NRS	**numerical rating scale**
RCT	**randomized controlled trial**
RoB	**Risk of Bias**
SMD	**standardized mean difference**
VAS	**visual analog scale**

Search strategy

The strategy had 2 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]; keywords for intervention were "Prolotherapy" [MeSH] OR dextrose [all fields] OR prolotherapy [all fields]. Search keys are summarized in appendix 1 (available online only at http://www.archives-pmr.org/).

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 1 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 but 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] Inactive control was defined as no treatment, standard care, or a waiting list control, and these included watchful waiting, bracing, and usual care. Active control was defined as the use of different injection solutions or a different kinds of therapies, 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 analog scale (VAS 0-100 mm), numerical rating scale (NRS 0-10), or algometry. Secondary outcomes included handgrip strength in kilograms,[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; www.covidence.org). Two reviewers (M.T.Z., R.W.S.S.) 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 5 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 2 reviewers (M. T.Z., R.W.W.S.); any discrepancy was resolved by a third reviewer (V.C.H.C.).

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 Patient-Related Tennis Elbow Evaluation cumulative score, and grip strength separately. Evidence was 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% confidence interval [CI], >0.8 for standardized mean difference [SMD] and > minimal clinically important difference [MCID] for mean difference [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 were fewer 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 v5.4)[a] 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 were summarized as SMDs with 95% CIs. 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 was used to measure outcomes sharing the same unit of measure, and its potential clinical significance was interpreted based on the 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^2 was calculated to quantify the degree of heterogeneity across studies. I^2 <25%, 25%-50%, and >50% indicate 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, 8 full texts met the inclusion criteria and were included for descriptive synthesis,[24-26,47-51] among which 5 were included in the quantitative synthesis procedure[24-26,50,51] (fig 1). Among the 3 that were not included in the quantitative synthesis, 1 study had no available data for extraction at 12-16 weeks,[52] and 2 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 8 included studies are 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 postenrollment. The injection frequency ranged from a single injection to 4 injections, weekly to 4 weeks apart, with dextrose concentration varying from 12.5% to 50%.

Risk of bias assessment

Overall, 87.5% of outcomes were scored as having "some concerns" (7/8), and 12.5% of outcomes were rated as having high risk of bias (1/8; fig 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] and 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 are summarized in appendix 2 (available online only at http://www.archives-pmr.org/).

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

In this comparison, 4 RCTs (n=183) were eligible for pooling.[24-26,51] VAS and NRS were reported, with SMDs calculated in the random effects 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=.04) and moderate heterogeneity (I^2=49%; fig 3a).

DPT vs active controls on DASH cumulative score at 12 weeks

In this comparison, 3 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<.001) and low heterogeneity (I^2=0%; fig 3b).

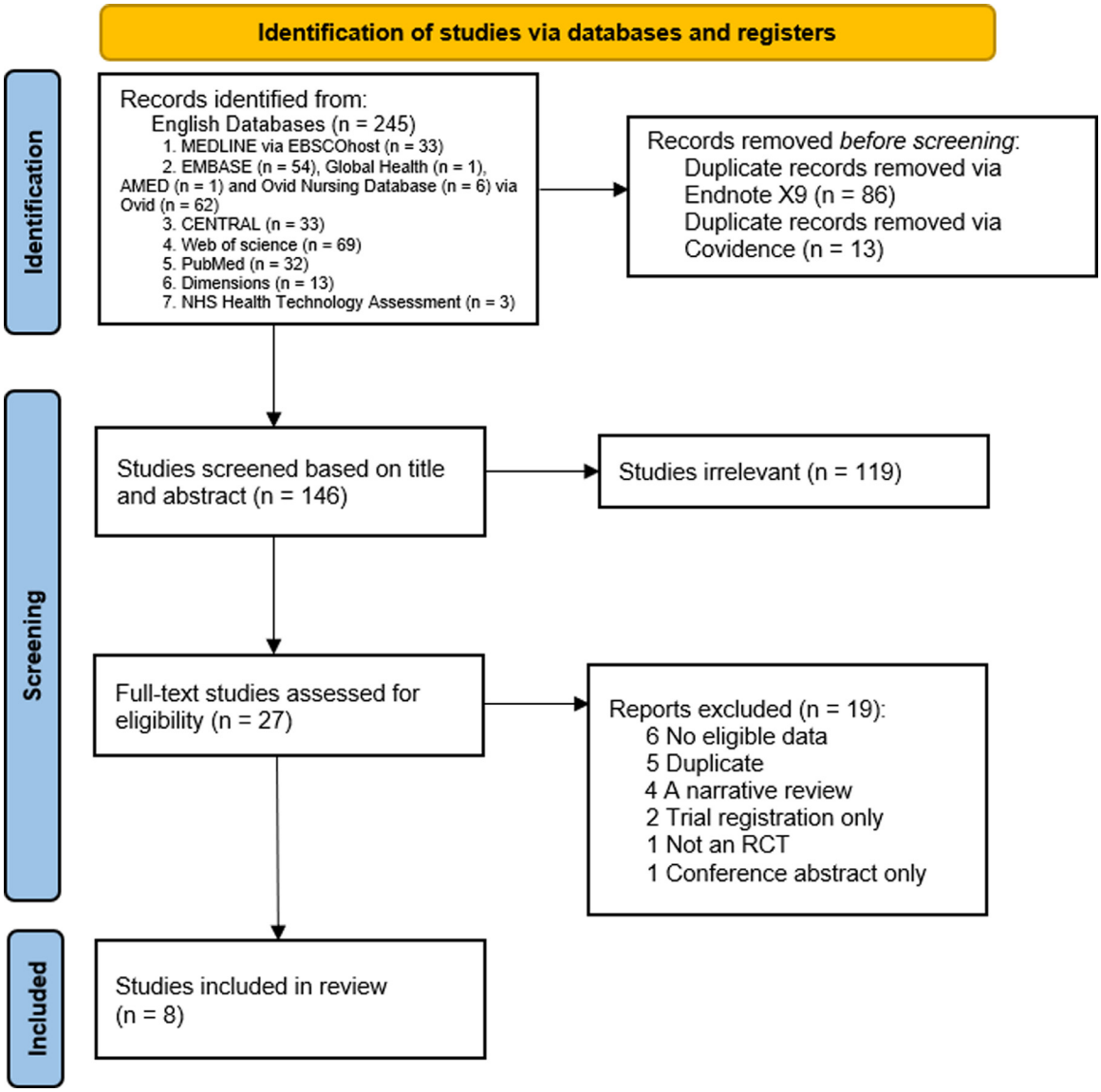

Fig 1 Flowchart of studies selected according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

DPT vs active controls on PRTEE cumulative score at 12 weeks

In this comparison, 2 RCTs (n=123) were eligible for pooling.[24,51] The same scale PRTEE scores 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*=.70) and moderate heterogeneity (I^2=42%; fig 3c).

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

Two RCTs (n=105) were eligible for pooling; a dynamometer was used in 1 trial to assess grip strength, and 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*=.90) and high heterogeneity (I^2=80%; fig 3d).

Adverse events

Injection side effects were reported in 7 of the 8 included trials. One trial reported that a DPT participant developed neuropraxia of the posterior interosseous nerve after the fourth treatment, but symptoms resolved in 3 months and there were no further negative effects; another DPT participant developed painful bruising over the forearm after the second treatment that resolved in 2 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 1 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, available online only at http://www.archives-pmr.org/). The assessment showed low certainty for DPT compared with active controls in reducing pain intensity and moderate certainty in improving DASH cumulative score. The assessment showed very low to low certainty on PRTEE cumulative score and grip strength.

Table 1 Characteristics of the 8 included studies.

Study	Sample Size	Sample Analyzed	Intervention Group	Control Group(s)	Mean Age (SD)	Female (%)	Injection Site(s)	Dextrose Vol/Inj.(mL)	Injection Frequency	Outcomes	Assessment Time Point	Duration
Ahadi et al[52]	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 wk	8 wk
Akcay et al[24]	60	50	Gp A (n=23): 15% dextrose	Gp B (n=27): 1.5 cc saline (0.9% NaCl)	Gp A: 48.1 (8.9) Gp B: 46.7 (8.3)	74.00%	Lateral epicondyle, annular ligament, and supracondylar ridge	1.5	0, 4, 8 weeks	VAS pain intensity (0-10 cm) PRTEE DASH (0-100) Pain-free handgrip strength	0, 4, 8, 12 wk	12 wk
Apaydin et al[25]	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 sensitive point in the lateral epicondyle	5	Gp A: 0, 3, 6 weeks Gp B: 0 wk	VAS (0-10 cm) Q-DASH (0-100) Pain-free grip strength	0, 6, 12 wk	12 wk
Bayat et al[26]	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 injection	VAS (0-10 cm) Quick DASH (0-100)	0, 4, 12 wk	12 wk
Carayannopoulos et al[48]	24	17	Gp A (n=8): 1.0 mL of procaine, 0.9 mL of P2G (phenol 1.2%, glycerine 12.5%, and dextrose 12.5% in sterile water) plus 0.1 mL sodium morrhuate	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 B: 46 (5.3)	64.71%	Lateral epicondyle of the humerus (first to the radial side of the annular ligament at the margin between the radial 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)	2	0, 4 wk	VAS (0-10 cm) QVAS DASH (0-100) Pain-free and maximum grip strength	0, 4, 12, 24 wks	24 wk
Rabago et al[49]	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 (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)	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 palpated tenderness and ultrasound-documented pathology	10	1, 4, 8 wk	PRTEE (0-100) Pain-free grip strength	0, 4, 8, 16, 32 wk	32 wk
	24	20			45.7 (10.7)	50.00%		0.5				52 wk

(*continued on next page*)

Table 1 (*Continued*)

Study	Sample Size	Sample Analyzed	Intervention Group	Control Group(s)	Mean Age (SD)	Female (%)	Injection Site(s)	Dextrose Vol/Inj.(mL)	Injection Frequency	Outcomes	Assessment Time Point	Duration
Scarpone et al[50]			Gp A (n=10): 10.7% dextrose (solution consisting of 50% dextrose, 5% sodium morrhuate, 4% lidocaine, and 0.5% sensorcaine). The study pharmacist mixed the following 35 mL sterile solution: 7.5 mL 50% dextrose, 5 mL of 5% sodium morrhuate, 2.5 mL 4% lidocaine, 2.5 mL 0.5% sensorcaine, and 17.5 mL normal saline. The solution is 10.7% dextrose and contains 14.7% sodium morrhuate by volume)	Gp B (n=10): 0.9% saline			Supracondylar ridge Lateral epicondyle Annular ligament		3 injections; 0, 4, 8 wk	NRS resting elbow pain (0-10 Likert scale) Resting grip strength Isometric resistance strength	0, 8, 16, 52 wk	
Yelland et al[51]	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; that is, over the lateral epicondyle, supracondylar ridge, radial head, lateral collateral and annular ligaments, and the common extensor tendon and musculotendinous junction	0.5-1.0	4 injections; 4-weeks apart (0.4,8.12 wk)	PRTEE GIC NRS pain severity at rest (0-10) NRS the worst pain severity (0-10) Pain-free grip strength EQ-5D-3 L	0, 6, 12, 26, 52 wk	52 wk

Abbreviations: EQ-5D-3L, EuroQol-5 Dimension 3-level version; GIC, global impression of change; Gp, group; PPT, pressure pain threshold; PRTEE, Patient-Rated Tennis Elbow Evaluation; QVAS, Quadruple Visual Analog Scale.

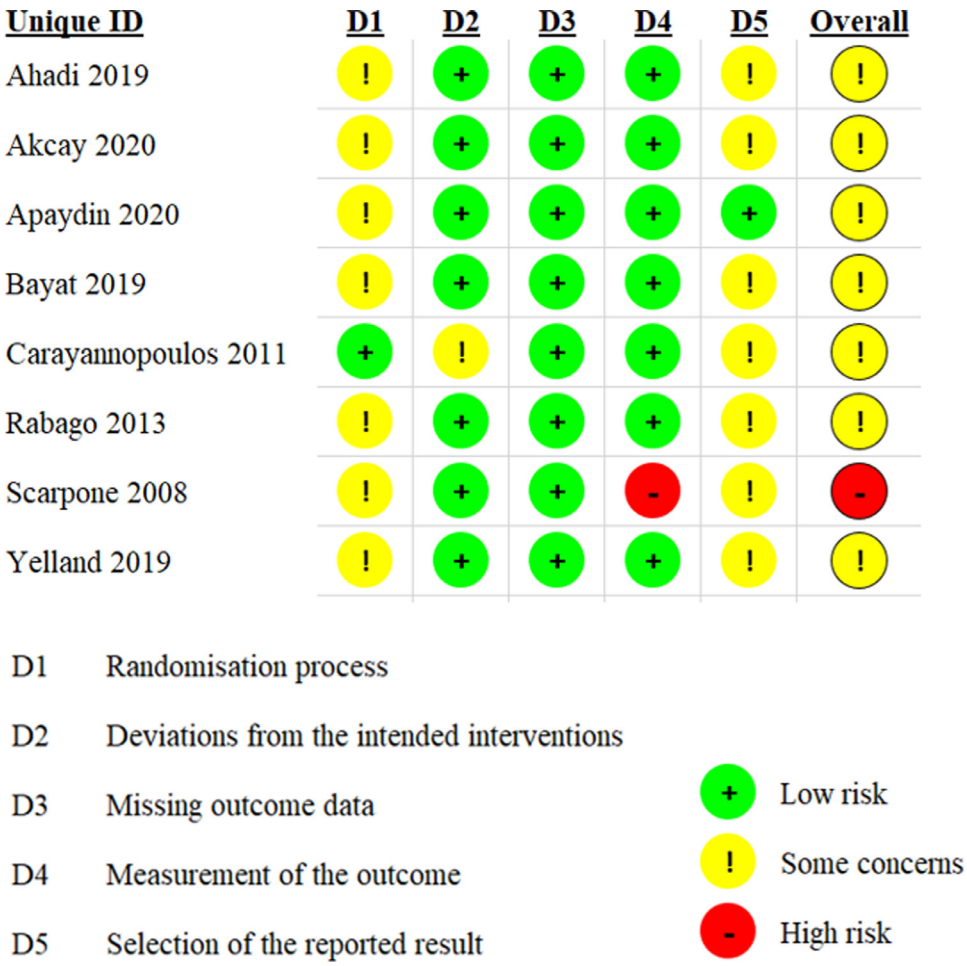

Fig 2 Quality assessment of included studies.

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 postenrollment, 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 because only 1 trial used waitlist as the control group.[49]

Compared 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 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 platelet-rich plasma 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 upregulation of pro-inflammatory markers, including interleukin 8, cyclooxygenase 2, and prostaglandin 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 increased energy absorption when compared with saline controls.[21,22] Dextrose solution hyperpolarizes nerves by opening their potassium channels, thereby decreasing signal transmission in nociceptive pain fibers.[57] In addition, glucose solutions may work by blocking transient receptor potential vanilloid type 1, thus reduce the action potentials and the release of substance P and calcitonin gene-related peptide, which theoretically could minimize neuropathic pain.[58,59]

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

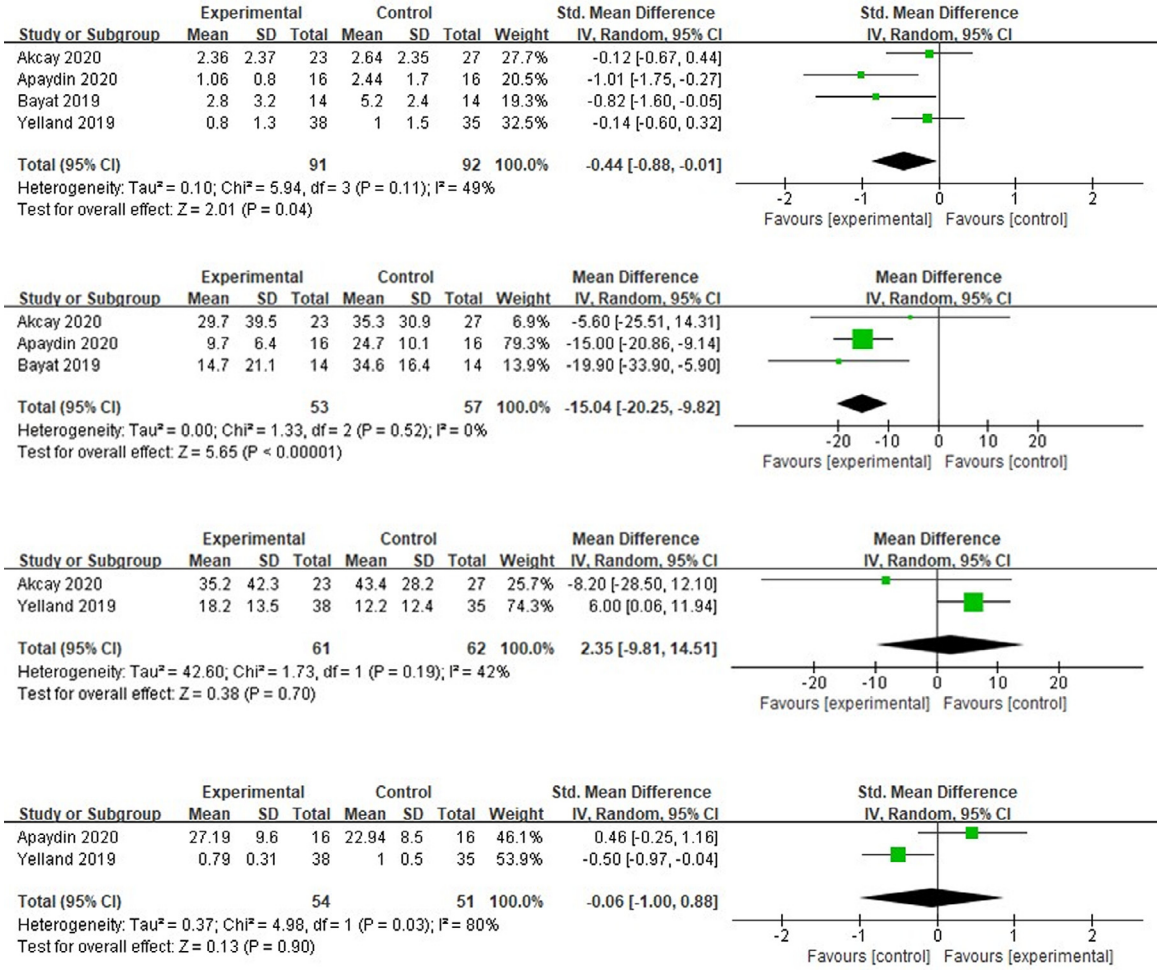

Fig 3 (a) Dextrose vs active controls on pain intensity (including VAS and NRS score) at 12 weeks. (b) Dextrose vs active controls on DASH cumulative score at 12 weeks. (c) Dextrose vs active controls on PRTEE cumulative score at 12 weeks. (d) Dextrose vs active controls on grip strength via dynamometer at 12-16 weeks.

Study limitations

There were several limitations of the current study. The number of studies included 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

Our systematic review and meta-analysis found that DPT outperformed active controls for improving pain intensity and function and 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 nonsurgical 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.

Supplier

a. Review Manager version 5.4; The Cochrane Collaboration.

Keywords

Meta-analysis; Pain; Prolotherapy; Rehabilitation; Systematic review; Tennis elbow

Corresponding author

Regina Wing-Shan Sit, MD, Clinical Associate Professor, Postgraduate Education Centre, Prince of Wales Hospital, 30-32 Ngan Shing Street, Rm 404, Sha Tin, New Territories, Hong Kong, China *E-mail address:* reginasit@cuhk.edu.hk.

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