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A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet rich plasma

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Abstract

Objective—To appraise existing evidence for prolotherapy, polidocanol, autologous whole blood and platelet-rich plasma injection therapies for lateral epicondylosis (LE)

Design—Systematic Review

Data sources—Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine. Search strategy: names and descriptors of the therapies and LE.

Study Selection—All human studies assessing the four therapies for LE.

Main results—Results of five prospective case series and four controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood and 1 platelet-rich plasma) suggest each of the four therapies is effective for LE. In follow-up periods ranging from 9 to 108 weeks, studies reported sustained, statistically significant($p<0.05$) improvement on visual analog scale primary outcome pain score measures and disease specific questionnaires; relative effect sizes ranged from 51% to 94%; Cohen's d ranged from 0.68 to 6.68. Secondary outcomes also improved, including biomechanical elbow function assessment (polidocanol and prolotherapy), presence of abnormalities and increased

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vascularity on ultrasound (autologous whole blood and polidocanol). Subjects reported satisfaction with therapies on single-item assessments. All studies were limited by small sample size.

Conclusions—There is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood and platelet-rich plasma injections in the treatment of LE. Rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue injury/healing-responsive biomarkers, are needed to determine long-term effectiveness and safety, and whether these techniques can play a definitive role in the management of LE and other tendinopathies.

Keywords

lateral epicondylosis; prolotherapy; polidocanol; platelet rich plasma

INTRODUCTION

Lateral epicondylosis (LE) ("tennis elbow") is an important condition of the upper extremity with an incidence up to 4–7/1000 patients per year[1–3] with substantial impact on athletes and workers. [4] 5 A subset of patients is refractory to non-surgical therapy including relative rest, eccentric exercise and corticosteroid injections and suffer long-term pain and disability on average lasting for six months to two years, regardless of therapy.[6] 7 Our understanding of the pathophysiology of lateral elbow overuse injury has changed in recent years.[8–11] The pathophysiologic hallmark of tendinopathy is the presence of degenerative changes, including neovascularity and disorganized collagen fibers.[9] 12 The precise cause of degeneration and pain in patients with a tendinopathy is not clear; mechanical, vascular, neural and "failure of healing" etiological models have each been proposed.[13]

Treatment approaches for LE vary widely and lack definitive evidence. Non-steroidal anti-inflammatory drugs and corticosteroid injections have traditionally been used but have not been shown to be more effective than watchful waiting in the long-term.[14] 15 Eccentric exercise regimens have shown some efficacy compared to age-gender-activity matched controls, though a sub-cohort of patients remain refractory.[16] Other non-surgical therapies have been evaluated for LE refractory to such conservative measures; none have shown to be consistently effective. [17–19] Polidocanol, prolotherapy, autologous whole blood and platelet rich plasma (PRP) injection therapies have reported promising outcomes for LE and other sport-related tendinopathies.

Polidocanol is a vascular sclerosant. In treating tendinopathy, it is used to sclerose areas of high intra-tendinous blood flow, sometimes termed "neovessels", which are seen histopathologically[12] and *in vivo* under high resolution ultrasound with color Doppler. Neovascularity is thought to be associated with the underlying mechanism of LE and other overuse tendinopathies,[20] 21 though whether it is a causal agent in the pathophysiology of tendinopathy is not clear.[22] A recent study reported that sustained sclerosis of neovascularity in LE was a good predictor of positive clinical effect at 2 years.[23] Several RCTs and prospective case series have reported positive effects of polidocanol therapy for patellar, epicondylar and Achilles tendinopathies.[24–26]

The use of prolotherapy dates to the 1930s,[27] when it was developed for pain associated with presumed ligament laxity. Although several injection agents have been used, hyperosmolar dextrose and morrhuate sodium (also a vascular sclerosant) are the most popular[28] and best studied agents. A recent systematic review identified 42 studies, over 50% of which evaluated prolotherapy for back pain, the remainder largely for painful conditions such as osteoarthritis and injuries associated with associated with ligament laxity.[29] Prolotherapy has also been used to treat tendinopathy of elite athletes[30] and LE.[31]

Autologous whole blood and the blood product PRP have been used as injectants for tendinopathy with the aim of providing cellular and humoral mediators to induce healing in areas of degeneration. Autologous whole blood injections have been used for medial[32] and lateral epicondylosis[33] and plantar fascititis.[34]

Platelet Rich Plasma is prepared from autologous whole blood, which is centrifuged to concentrate platelets in plasma. The intention is to augment the native healing process at the site of pain through the action of platelet-derived growth factors (PDGF). Platelets contain at least 6 PDGFs vital to bone and soft tissue healing (Table 1). The basic and clinical science of PRP has been reviewed.[35] Since the early 1990s PRP has been used for its purported ability to improve soft tissue healing and bone regeneration. The use of PRP is being intensely studied and reports suggest that clinical use is increasing rapidly for LE,[36] rotator cuff repair,[37,38] acute and chronic muscle strain, muscle fibrosis, ligamentous sprains, and joint capsular laxity (David Crane, MD, personal communication).

These therapies, which target the diseased tendon tissue directly, may interrupt the degenerative cycle associated with tendinopathy and allow the return of the native healing process, ultimately leading to improvement in clinical outcomes. None have been directly compared in any trial setting, but each has been assessed for LE. Because of the potential for prolotherapy, polidocanol, whole blood and PRP injection therapies to be effective for tendinopathies, we undertook a systematic review of the literature for each technique for the treatment of refractory LE.

METHODS

Inclusion criteria included: human clinical trials of any design involving pre- and post-treatment assessment evaluating any of the four injection therapies for LE. A literature search was performed by the lead author (DR) and library staff of the following electronic databases: Medline (Ovid Web, 1950–2008 and Medline In-process & Other Non-Indexed Citations), Embase (1974–2008), CINAHL (1982–2008), the Cochrane Central Register of Controlled Trials (Through 3rd quarter 2008) and Allied and Complementary Medicine (1985–2008). Search strategies utilized the names of each intervention and the names of the injectants (Table 2). Reports not cited in the databases above were searched used the Google© search engine and the National Institutes of Health (NIH) CRISP electronic database using relevant anatomical descriptors and therapy names. The reference lists of identified studies were reviewed to identify potentially eligible studies. E-mail or phone contact was attempted with relevant author(s) or Principal Investigator(s) of included articles or abstracts when additional information was needed.

Identification of eligible studies

The titles and abstracts of all identified studies were screened by the study librarian and the lead author (DR). Studies whose title and abstract clearly indicated that the paper met criteria were reviewed. A description of excluded studies follows.

Data extraction—The data collection strategy for the methods and results sections of identified papers was determined a priori. Data from prospective case series was extracted by the lead author (DR). Two unblinded authors (DR, TB) assessed each controlled study. Data were extracted using a pre-existing technique.[39] The RCT strength was assessed using the Delphi[40] controlled trial internal validity assessment. Disagreements were resolved by consensus. Using these instruments, the methods and results of each study were described and an overall quality score assigned. Where possible, several measures of "effect size" at various follow-up time points were calculated by the authors: 1) “Percent improvement” was calculated for all intervention arms as the change in pain score divided by the baseline score multiplied by 100%. 2) Cohen's d was used as published or, if not provided, was calculated according to one of two formulas: a) for controlled trials, $d = [M_1 - M_2] / SD_{pooled}$, where M_1, M_2 were the means in the two groups, and $SD_{pooled} = \sqrt{[(SD_1^2 + SD_2^2) / 2]}$; b) for pre-post assessments, d = [mean of the pre-post difference] / [SD of the mean]; if data for formula 'b' was not available, then formula 'a' was applied, when possible. 3) In one study,[33] effect size was estimated based on the Z value of the Wilcoxon Signed Rank Test according to the formula: $Z/\sqrt{N}$, where N equals the number of observations over the two time points.[41] An overall evidence grade for each technique was assigned by the lead author (DR) based on the Strength of Recommendation Taxonomy criteria.[42]

RESULTS

The search identified 21 reports as possibly relevant; the abstract of each was reviewed. Nine studies met the eligibility criteria. Excluded studies were: general reviews (3), surgical (1), basic science (1), for different indications (3), editorials (2) or assessed a non-reviewed therapy (1). Differences in the methods of the four therapies and in outcome measures used prevented pooling of data. Heterogeneity and inter-rater agreement of controlled study quality scoring were not formally assessed. First authors were queried about ambiguous elements of their studies. There was no significant disagreement between the raters.

Study Outcomes

We identified nine eligible reports, four controlled studies and five prospective case series evaluating effects of prolotherapy (three), polidocanol (two), autologous whole blood (three) and PRP (one) therapies for LE assessing 208 adult subjects (Table 3,Table 4). The common primary inclusion criteria were elbow pain for a minimum of two months and being refractory to one or more conservative therapies. The subjects were 19–66 years old, diagnosed with LE due to variety of work and recreational activities. No study reported the inclusion of elite athletes. Subjects had an average pain duration ranging from 2 to 102 months. Subjects in three studies [25 33 43] underwent ultrasound evaluation as part of the diagnosis and injection protocol and had areas of structural change and neovascularization within the common extensor tendon. The controlled studies[25 31 36 44] were of moderate to high quality, scoring 5–9/9 on the Delphi assessment. All controlled studies compared active solution to a comparison solution with either vasoactive control agents (lidocaine/epinephrine or bupivacaine/epinephrine[25 36]or saline.[31] The primary outcome of each study was pain on a visual analog scale (VAS) or pain questionnaire[44] though the denominator and specific issue addressed varied slightly. Improvement ranged from 51%[25] to 94%[45] for the active groups compared to baseline status; Cohen's d effect size ranged from 0.68[33] to 6.68[31], indicating a strong effect. Cohen's d was not calculated for some studies due to insufficient data.[25 45 46 36]

In a prospective case series[43] subjects receiving US-guided polidocanol treatment, VAS scores improved by 37% at 3 months ($p<0.05$) and 55% by 8 months ($p<0.01$). Grip strength significantly improved at 3 and 8 months. Structural defects and vascularity on US were improved at 8 months. In a subsequent double blind RCT, Zeisig et al.[25] compared polidocanol to vaso-constrictive lidocaine/epinephrine injections. Both groups improved their VAS pain scores at 3 months, without significant differences between the groups. Three months following the first treatment session, subjects in both study groups who were unsatisfied with clinical results were offered an additional injection session with polidocanol. Follow-up at 12 months after enrolment showed that additional polidocanol injections improved VAS scores by 51% and 47% compared to baseline in subjects receiving initial polidocanol and epinephrine injection respectively.

In two RCTs,[31 44] and one prospective case series,[45] subjects received either prolotherapy or normal saline. Active subjects in Scarpone et al. reported improvement of 90% at 16 weeks compared to 22% for controls (p<0.001), with four prolotherapy subjects reporting complete pain resolution. In a small RCT, Glick et al, subjects reported 66% improvement on a disease specific questionnaire compared to 11.5% for controls (p=0.09). In a prospective case series, Lyftogt[45] reported 94% improvement compared to baseline scores using a novel subcutaneous injection technique (p< 0.05).

Three prospective case series assessing autologous whole blood were identified.[33 46 47] Each study reported significant (p<0.05) improvement compared to baseline: Edwards et al. reported 88%,[47] Gani et al. reported 64% and[46] Connel et al.[33] reported a median score of "0".

In a non-randomized controlled trial[36] comparing a single treatment session of PRP to control injections., PRP subjects improved by a mean of 81% by 27 weeks. PRP subjects were further followed to a mean of 25.6 months, at which point the authors reported 93% pain reduction compared to baseline. Controls reported 17% improvement at 4 weeks; 3 of 5 control subjects dropped out before the 8 week follow-up and the remaining 2 Control subjects were not followed further.

Secondary outcome measures also improved in all eight studies. Mishra et al.[36] reported significant improvement on the Mayo Elbow-Performance Index. Each study assessing whole blood injections reported significant improvement in Nirschl scores.[33 46 47] Zeisig et al.[25] and Scarpone et al.[31] reported significant improvement on maximal grip strength compared to baseline in the intervention groups. Scarpone et al. also reported improved isometric strength in the prolotherapy group compared to controls. Zeisig et al.[43] and Connell et al.[33] reported decreased structural defects and neovascularity on US, though these were not reliably correlated to clinical gains. Treatment satisfaction on single-item assessments was reported by 78% of the "polidocanol only" subjects at 12 months,[25] by 93% of the PRP subjects at 25.6 months[36], and by 100% of subjects in Lyftogt et al.[45] Scarpone et al.[31] reported that prolotherapy subjects qualitatively reported maintenance of treatment effects at 12 months.

DISCUSSION

Prolotherapy, polidocanol, autologous whole blood and PRP injection therapies have received attention in the treatment of tendinopathies among elite athletes and primary care patients. This is the first systematic review to compare these techniques for a single condition, LE. Each of the studies reviewed is small, and their methodological limitations prevent a consensus recommendation on the use of any of the three therapies compared to another at this time. However, the large effect sizes reported by all studies are compelling and suggest several areas of clinical, theoretical and research interest.

Clinical Implications

As a technique that places injectant on or near a degenerative area of the tendon-bone insertion, each injectant appears safe. Though not powered to detect rare local or systemic negative effects, no study evaluating any of these therapies for musculoskeletal conditions has reported serious adverse events. Two systematic reviews of prolotherapy [29 48] and a study of negative consequences of prolotherapy[28] reported only minor side effects consistent with injection trauma, suggesting that the prolotherapy injectants themselves are safe. Though vascular sclerosants can theoretically cause tissue necrosis, this was not reported in these studies. The transmission of blood-borne disease is a possibility in each therapy, and underscores the need for universal precautions, including the use of gloves and appropriate handling and disposal of medical waste.

With moderate-to-large effect sizes that far exceed minimal clinically relevant effect sizes for chronic pain,[49] and which are sustained over 12[25 31] to 25 months[36]compared to baseline or comparison groups, each technique appears potentially effective for refractory LE, thus expanding treatment options for patients who have failed conservative care. In one author's clinic (EZ) the stepwise treatment algorithm for LE is: 1) conservative measures including eccentric exercise, 2) polidocanol injections, and 3) surgery, which, in the author's experience, is rarely required. A similar algorithm has been reported for Achilles tendinopathy.[50]

The ease of clinical application of these techniques varies. Each requires routine medical knowledge of diagnostic, anatomical and joint injection skills. However, the procurement and processing of the injectants, and the required assessment associated with each therapy vary. For example, polidocanol therapy calls for ultrasound and color Doppler exam and specialized skills to visualize increased vascularity. PRP therapy requires investment in a centrifuge and blood processing equipment, and corresponding skills. Individual characteristics of the platelet preparation differ slightly between companies based on a number of factors; several reviews are available.[35 37] Prolotherapy has limited start-up costs and is the easiest to implement. However, it may more labor-intensive; in the reviewed studies, it required three treatment sessions, whereas the other three therapies typically used one or two treatment sessions.

Theoretical Implications

The cause of pain in LE and the precise mechanism of action of the four injectants are unclear. The reviewed studies offer an opportunity to address aspects of both issues. Researchers have suggested that clinical effects of these therapies may in part result from the compressive effects of injected solutions, needle trauma, and irritant effects of blood.[25 29] The studies however, suggest that the "active" group injectants themselves provide the majority of therapeutic effects. No significant volume-related effect of comparison saline or dilute epinephrine injection was found in three RCTs.[31 44 36] Similarity in outcomes in Zeisig et al.[25] may be explained by the actions of the two solutions: vasosclerosis may have a slightly greater effect on the neurovascular milieu than does temporary vasoconstriction. However the study design did not allow additional epinephrine injections so whether polidocanol is more effective than epinephrine for LE remains unclear. Mishra et al. found no significant effect from mild pre-injection fenestration. It is unclear whether the more active fenestration performed by Connell et al. influenced outcomes, as no other study reported such a pre-injection procedure.

The notion that these injectants exert a biological effect independent of needle trauma or volume-related effects is consistent with clinical, animal model and *in vitro* evidence. Recent clinical studies documented that areas of increased vascularity are associated with painful LE,[51] have significant sensory innervation, and are linked with higher concentrations of the pain modulators glutamate and calcitonin gene-related peptide.[52] Sclerosing of such structures in Achilles and patellar tendinopathy have also led to reduction in pain.[24 26]

Prolotherapy with dextrose with or without morrhuate sodium has been reported to decrease pain and improve function in a variety of tendinopathies.[53 54 30] The historical hypothesis that prolotherapy causes an inflammatory response leading to reduced tendon and ligament laxity[55] has not been confirmed. Two recent studies did not detect increased inflammation or decreased laxity following prolotherapy in a rat model.[56 57] Morrhuate sodium is in the same chemical class as polidocanol and likely acts as a vascular sclerosant. Animal model data support a biological effect. Rabbit medial collateral ligaments injected with morrhuate sodium were significantly stronger (31%), larger (47%), thicker (28%) and had larger collagen fiber diameter (56%) than saline-injected controls.[58] Rat patellar tendons injected with morrhuate sodium were able to withstand a mean maximal load of 136% of the uninjected control tendons.[59] Hyperosmolar dextrose is also a mild vascular sclerosant, though its potential effect in tendinopathy is not well understood. A hyperosmolar glucose environment has been shown to increase platelet-derived growth factor expression and up-regulate multiple mitogenic factors[60 61,62] that may act as signaling mechanisms in tendon repair. Lyftogt has suggested that neurogenic inflammation[63] may contribute to pain in LE, and that subcutaneous injections of hyperosmolar dextrose target inflamed branches of the posterior antebrachial and medial antebrachial cutaneous nerves. (Lyftogt personal communication, 2008) However neither growth factor nor "neurosclerotic" effects have been confirmed in a tendinopathy model.

PRP injections make use of activated platelets which discharge bioactive signaling molecules including 3 adhesion molecules and 7 growth factors. A total of 21 of 28 clinical reports, largely from the maxillo-facial and wound care fields have reported positive PRP effects on bone and wound healing. However, many studies had a small sample size and used different methods for platelet processing thereby preventing definitive conclusions.[35] Most PRP-related *in vitro* and animal model science reports come from the orthopedic literature on bone healing and report a variety of cellular and growth factor effects of potential importance to tendon healing. [35] Studies assessing PRP effects for soft tissue healing showed increased anabolic gene expression in horse flexor tendons[64]and proliferation of tendon cells and production of VEGF.[65] 66 Two large animal studies have recently reported improved healing of the repaired dog and porcine cruciate ligaments following PRP therapy.[67] 68

Research implications

Basic science research is needed to elucidate the mechanism of action for each injection therapy. Sufficiently powered clinical trials should evaluate efficacy and effectiveness of each of the therapies compared to eccentric exercise and to each other. Research would benefit from the unification of outcome measures across these studies which should include clinically relevant, patient-reported and objectively assessed outcomes such as pain, function and disability. Assessment of tissue injury/healing-sensitive biomarkers may enhance our understanding of the processes underlying treatment efficacy. Existing preliminary data suggest these injection therapies have a disease-modifying potential; therefore, imaging studies, such as MRI and/or ultrasound with color Doppler may also be useful in addressing the mechanisms by which these agents promote healing. Whether results can be generalized across different patient populations (e.g. athletes and occupational workers) remains an important question to be answered. Larger studies assessing PRP, prolotherapy and autologous stem cell injection for LE are currently in progress (Personal communication: Allan Mishra, Ron Glick and David Connel)

CONCLUSIONS

Existing data for prolotherapy, polidocanol, autologous whole blood and PRP injection therapies for refractory LE suggest effectiveness, but are limited by lack of large definitive trials. These therapies appear safe and effective when performed by an experienced clinician. Positive results have been reported in case series, non-randomized and randomized studies with LE from a variety of sport and work-related causes. Future studies using validated clinical measures, and radiological, biomechanical and tissue injury / healing-responsive biomarkers as secondary outcome measures are needed to determine whether these injection techniques can play a definitive role in a cure for LE and other tendinopathies.

What is already known about this subject?

Therapies for lateral epicondylosis and other overuse tendinopathies are varied; none have been found to definitively reduce pain and improve function. Data suggestive of efficacy for prolotherapy, polidocanol, autologous whole blood and platelet rich plasma injections have been reported in limited, pilot-level studies but have not been directly compared.

What this study adds

This systematic review compares studies assessing prolotherapy, polidocanol, autologous whole blood and platelet rich plasma injections for a single tendinopathy, lateral epicondylosis. Nine studies document a large effect size for each technique; “percent change compared to baseline” and “Cohen’s d” ranged from 51% to 94%, and 0.68 to 6.68 respectively.

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Table 1

Synopsis of growth factors contained in platelet rich plasma.[35]

Growth Factor	Source	Function
Transforming Growth Factor-beta, TGF-β	Platelets, extracellular matrix of bone, cartilage matrix, activated TH1 cells and natural killer cells, macrophanges/monocytes and neutrophils	Stimulates undifferentiated mesenchymal cell proliferation; regulates endothelial, fibroblastic and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion; regulates mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophange and lymphocyte proliferation
Basic Fibroblast Groth Factor, bFGF	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenetic for mesenchymal cells, chondrocytes and osteoblasts
Platelet Derived Growth Factor, PDGFa-b	Platelets, osteoblasts, endothelial cells, macrophanges, monocytes, smooth muscle cells	Mitogenetic for mesenchymal cells and osteoblasts; stimulaltes chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis
Epidermal Growth Factor, EGF	Platelets, macrophages, monocytes	Stimulates endothelial chemotaxis/ angiogenesis; regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis
Vascular endothelial growth factor, VEGF	Platelets, endothelial cells	Increases angiogenesis and vessel permeability, stimulates mitogenesis for endothelial cells
Connective tissue growth factor, CTGF	Platelets through endocytosis from extracellular environment in bone marrow	Promotes angiogenesis, cartilage regeneration, fibrosis and platelet adhesion

Table 2

Search Strategy

Step	Search Strategy
1	Tennis Elbow.mp. or ((Tend?nopath*.mp. or tend?nitis or tend?nosis) and Elbow*).mp. or Lateral adj3 Epicondyl*.mp. or Chronic adj3 Elbow adj3 Pain.mp.
2	Sodium adj2 Morrhuate.mp. or Dextrose.mp. or Prolotherap*.mp. or Polidocanol*.mp. or ((Platelet adj1 Rich) adj3 Plasma).mp. or Autologous adj3 Injection*.mp. or ((Whole adj1 Blood) adj2 Injection*.mp. or Sclerotherap*.mp.
3	1 and 2

Table 3

Clinical Trials of Prolotherapy (PrT), Polidocanol (Pdl), Autologous Whole Blood (AWB) and Platelet Rich Plasma (PRP) injection therapies for LE. Results reported for a final follow-up unless stated otherwise.

Study /Type	Subjects	Intervention	Injectant / Control	Ancillary treatment	Follow-up / Outcome Measures	Results	*Effect size of Pain Score (Cohen's d and % improvement)*	Comments	Delphi score, x/9
Zeisig et al. 200825 Polidocanol RCT	36 (16 F); mean age 46 (27–66) yrs; LE pain for mean 21 months; failed one or more of: PT, eccentric PT, NSAIDs, steroid injections, orthotics, acupuncture, ultrasound, botox injections	Pdl: at 0 wks, and optional at 12 wks; U/S guided, to "neovessels"; after their 1st injection session (in Pdl or comparison group), all subjects were offered Pdl injections at 12 wks if unsatisfied with effects of 1st injection; 0.5–1 mL total	• Pdl: 10 mg/mL; • Active comparison group: lidocaine + epinephrine; optional Pdl injections at 12 wks (cross-over)	none	• 12, 52 wks; • exertional pain (0–100 VAS); maximum grip strength; subject satisfaction (0–100% scale)	• no between-group differences in pain score, grip strength or satisfaction; • compared to baseline, at 52 wks, pain improved (p<0.05) by 32 points in Pdl group, and 36 points in comparison group; • grip strength improved (p<0.05) for both groups at 52 wks; • mean subject satisfaction 80%	*Compared to baseline:* *• 12 wks: Cohen's d: N/A Pdl improved: 23%, Epinephrine improved 13%* *• 52 wks: Cohen's d: N/A; Pdl improved: 51% (p<0.05) Epinephrine/Pdl improved 47%*	at 12 wks, unsatisfied control subjects were crossed-over to Pdl injections, if desired	9
Zeisig et al. 200643 Polidocanol Prospective case series	11 (7F); mean age 46 (33–63) yrs; LE pain for mean 23 months; failed one or more of: PT (7), NSAIDs (11), steroid injection (7), orthotics (5), acupuncture (2), ultrasound (2)	Pdl: at 0 wks; 0.4–1.1 mL total	• Pdl: 10 mg/mL; Control: N/A	none	• 12, 35 wks; • exertional pain (0–100 VAS); maximum grip strength; structural defect (yes/no) & degree of vascularity (0–2 scale) on U/S; subject satisfaction (0–100% scale)	• pain improved by 28 points at 12 wks and 41 points at 35 wks (p<0.05); • grip strength, presence of structural defect and degree of vascularity improved at 12 and 35 wks (p<0.05); • mean subject satisfaction 83%	*Compared to baseline:* *• 35 wks: Cohen's d: 1.4 Improved: 55% (p<0.05);*	prospective case series	N/A
Scarpone et al. 200831 Prolotherapy RCT	24 (13 F); mean age 45.7 (19–62) yrs; LE pain for mean 1.9 yrs; failed	PrT: at 0, 4, 8 wks, to tender points at supracondylar ridge, lateral epicondyle	• PrT: 10.7% dextrose + 14.7% sodium morrhuate	none	• 8, 16, 52 wks • resting elbow pain (0–10 VAS); isometric strength; grip strength;	• at 16 wks, pain improved (p<0.05) by 4.6 points c/t baseline, and 3.6 points c/t control;	*Compared to baseline:* *• 8 wks: PrT Improved: 35% (p<0.05);*	lack of consistent, long-term follow-up; unconventional	8

Study /Type	Subjects	Intervention	Injectant / Control	Ancillary treatment	Follow-up / Outcome Measures	Results	*Effect size of Pain Score (Cohen's d and % improvement)*	Comments	Delphi score, x/9
	NSAIDs, relative rest, PT, 2 steroid injections	and annular ligament; 1.5 mL total	• Control: 0.9% Saline		continuity of improvement at 52 wks	• at 16 wks, isometric strength improved (p<0.05) c/t baseline and control; grip strength improved (p<0.05) c/t baseline; • at 52 wks, qualitative improvement c/t control	*Control improved 20%* • *16 wks* :PrT improved 90% (p<0.05), Control improved 22% *<u>Compared to controls</u>: PrT improved 68%; Cohen's d: 6.68:*	assessment of grip strength	
Glick et al. 2008 Prolotherapy RCT	8 (2F), mean age 50; LE pain for greater than 3 months	PrT: at 0, 3 and 6 wks to the lateral epicondyl and tender extensor tendon origin; 5 mL total	• PrT: 15% dextrose and 1% lidocaine •Control: 0.9% saline and 1% lidocaine	All subjects used at-home stretching	• 9 wks; McGill Pain Questionnaire (0–45), Physical Composite score of MOS SF-36	• McGill score improved (p=.086) by 7.75 points c/t baseline and 7 points c/t control • Physical Composite score improved (p=0.05) by 8.4 points c/t baseline and control. Cohen's d statistic calculated to be 1.57 and 1.78 for the McGill and MOS measures respectively	*<u>Compared to baseline</u>: • 9 wks: PrT Improved: 66% (p<0.05);Control improved 11.5% <u>Compared to controls</u>: • 9 wks: Cohen's d = 1.6 Improved: 54.5% (p<0.09);*	lack of disease-specific outcome measure, short follow-up period	7
Lyftogt 200745 Prolotherapy Prospective case series	20 (9F), mean age 39 (24–64) yrs; LE pain for mean 6 months	PrT: weekly sessions for mean 8 wks; to tender points at common extensor tendon; 0.5–1.0 mL total	• PrT: 20% glucose + 0.1% lidocaine • Placebo: N/A	modified daily activity	• weekly during intervention (mean duration of 7.2 wks); final follow-up at mean 19 months; • elbow pain (0–10 VAS); subject satisfaction (yes/ no)	• pain improved by 6.8 points c/t baseline (p<0.05); • 100% of subjects satisfied	*<u>Compared to baseline</u>: • mean 19 months: Cohen's d: N/A Improved: 94% (p<0.05);*	unconventional subcutaneous prolotherapy technique with 10–15 injections per session	N/A
Edwards et al. 200347 Autologous Whole Blood	28 (14F); LE pain for at least 3	AWB: at 0, 6 wks, and optional at 12	• AWB: whole autologous blood +	400 splint; 3 wks of motion restriction,	• every 6 wks for at least 26 wks	• pain improved by 5.5 points by a mean of 3 weeks	*<u>Compared to baseline</u>:*	prospective case series; no statistical comparisons reported	N/A

Study /Type	Subjects	Intervention	Injectant / Control	Ancillary treatment	Follow-up / Outcome Measures	Results	*Effect size of Pain Score (Cohen's d and % improvement)*	Comments	Delphi score, x/9
Prospective case series	months; failed 2 or more conservative therapies	wks; to extensor carpi radialis brevis; 2 mL total	2% lidocaine or 0.5% bupivacaine; • Control: N/A	then 3 wks of stretching exercises	(mean 9.5 months); • pain at rest (0–10 VAS); Nirschl scale (1–7)	after last injection. •Nirschl scale improved by 4.5 points at a mean of by a mean of 3 weeks after last injection	• *after 1st injection: Cohen's d: 1.7 Improved: 40% (p<0.05);* • *after 2nd injection: Cohen's d: 3.0 Improved: 88% (p<0.05);*		
Connell et al. 200633 Autologous Whole Blood Prospective case series	35 (12F); mean age 40.9 (26–62) yrs; LE pain for mean 13.8 months; failed each of: rest, PT, steroid injection	AWB: 0, 4 wks, and optional at 8 wks; U/S guided, to area of maximal structural discontinuity; 2 mL total	• AWB: autologous whole blood; • Control: N/A	• preinjection: 0.25% bupivacaine, 2 mL, injected to common extensor tendon, and 1 minute of dry-needling (fenestration)	• 4, 26 wks • pain (0–10 VAS); Nirschl scale (1–7); U/S assessed tendon thickness, hypoechogenicity, neovascularity; treatment satisfaction (yes/no)	• pain: median score 9, 6 & 0 at baseline, 4 & 26 wks, respectively; • Nirschl scale: median score 6, 4 & 0 at baseline, 4 & 26 wks, respectively; • U/S: mean tendon thickness, hypoechogenicity and neovascularity improved (p<0.001) • 91% of subjects satisfied	*–<u>Compared to baseline</u>: • 4 wks: Cohen's d: 0.68; • 26 wks: Cohen's d: 0.72*	prospective case series; raw data, mean scores and statistical comparisons for some of the outcomes not provided	N/A
Gani et al. 200746 Autologous Whole Blood Prospective case series	26 (16 F); mean age 34 (21–54) yrs; LE pain for mean 2.1 yrs; failed rest, NSAIDs, activity modification, steroid injection	AWB: at 0 wks, and optional at 6 wks	• AWB: whole autologous blood; • Control: N/A	sling for 1 week, then rest and stretching exercises; no heavy lifting for 3 wks	• weekly, up until 35 wks on average; • pain (4-point Likert scale); Nirschl scale (1–7)	• pain improved (p<0.05) by 2.1 points at 35 wks; • Nirschl scale improved (p<0.05) from mean score 5.5 to 2.1 at 35 wks	*<u>Compared to baseline</u>: • after up to 2 injections: Cohen's d: N/A Improved: 64% (p<0.05);*	prospective case series; unconventional Likert scale as primary outcome	N/A
Mishra et al. 200636 Platelet Rich Plasma Non-randomized controlled trial	20 adults; 15 PRP subjects: mean age 48.1 yrs, LE pain for mean	PRP: single injection at 0 weeks	• PRP: pH 8.4, Approximately 3.3 million platelets per treatment session	• stretching exercises for two wks, then formal strengthening	• 8, 26, 108 wks; • exertional pain (0–100 VAS); Mayo Elbow Performance Index; % subjects	• at 8 wks, pain improved (p<0.05) by 33 points c/t control; c/t baseline, pain improved	*<u>Compared to baseline</u>: • 8 wks: **Cohen's** d: N/A Improved: 60% (p<0.05);*	non-randomized design; 3 of 5 control subjects left study at 8 wks; injected local anesthesia used in both groups; 108-week	5

Study /Type	Subjects	Intervention	Injectant / Control	Ancillary treatment	Follow-up / Outcome Measures	Results	***Effect size of Pain Score (Cohen's d and % improvement)***	Comments	Delphi score, x/9
	15.3 months; 5 control subjects: mean age 42 yrs, LE pain for mean 11.8 months; failed one or more of: NSAIDs, PT, bracing, steroid injection		• Control: bupivacaine + epinephrine	exercise program for 2 wks	satisfied with therapy	($p<0.05$) by 47, 71 and 80 points at 8, 26 and 108 wks, respectively; • Mayo Index improved by 19 points c/t control and 26 points c/t baseline ($p<0.05$) at 8 wks, and by 36 points c/t baseline at 26 wks; • 93% of subjects satisfied	• *27 wks: Cohen's d: ; N/A Improved: 81% ($p<0.05$)* *<u>Compared to controls</u>:* • *8 wks: N/A*	Mayo score not reported	

AWB: autologous whole blood; c/t: compared to; LE: lateral epicondylosis; N/A: non-applicable; NSAIDs: non-steroidal anti-inflammatory drugs; Pdl: polidocanol; PRP: platelet rich plasma; PrT: prolotherapy; PT: physical therapy; U/S: ultrasound; VAS: visual analog scale; wks: weeks; yrs: years

*Median scores reported, percent change therefore not calculated; Cohen's d calculated using reported Z statistic.

Table 4

Comparison of the Strength of Evidence Taxonomy (SORT) recommendation[42] and methodological considerations for each injection therapy when used to treat lateral epicondylosis, as practiced in assessed papers

Injectant	*SORT recommendation*	Anatomical evaluation	Injectant preparation	Added injectants	Injection technique	Volume injected	Injection Schedule
Polidocanol	***2B***	Palpatory exam, U/S and Color Doppler exam; elbow structures are examined while seated, with arm resting on a table in 70–80 degrees of elbow flexion and wrist pronation	None; stock polidocanol 10 mg/mL solution used	None	US and Color Doppler guided injections at the common extensor origin at the lateral epicondyle. The aim is to inject polidocanol intravascularly, however, due to the small size of neovessels, the solution may be delivered perivascularly.	0.4–1.1 mL; one injection, using 3–5 needle sticks to ensure coverage of neovessels	1–2 injection sessions, approximately 3 months apart
Autologous Whole Blood	***3C***	Palpatory exam ± U/S exam	2 mL autologous whole blood collected at the time of injection	Topical anesthetic	Injection to undersurface of extensor carpi radialis brevis[47, 46] or area of maximal tendon disruption on U/S exam[33]	2 mL	Study dependent; 1–3 injection sessions, approximately 1 month apart
Platelet Rich Plasma	***2B***	Palpatory exam	Preparation of syringes with anticoagulant, then 20–60 mL of whole blood is drawn from peripheral vein Blood is centrifuged Preparation of the injection site with local anesthetic	Proprietary, kit - dependent; anticoagulant	U/S-guided single injection, using 5–7 needle sticks, 1 cm distal to the origin of the common extensor tendon	1mL per cm^2 of involved tissue, up to total of 2–3 mL	Single injection session
Prolotherapy	***1B***	Palpatory exam	None; injectant prepared from stock solution of 50% dextrose and 5% morrhuate sodium	Saline and topical anesthetics: lidocaine and sensorcaine	Injection at tender enthuses of ligament and tendon structures at the lateral epicondyle and supracondylar ridge; precise location and number of injections per session as well as the number of sessions per treatment course are patient-specific, determined by exam	0.5 mL per injection, 3–5 injections per session	3 monthly sessions

U/S: ultrasound