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ORIGINAL ARTICLE

Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial

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Abstract
Purpose To compare the advantages of prolotherapy in the treatment of first carpometacarpal osteoarthritis (OA) with those of corticosteroid local injection in the short and long term.
Methods We performed a randomized controlled trial from March 2010 to March 2011 in an outpatient clinic at a university hospital. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to two groups. For the corticosteroid group, after 2 monthly saline placebo injections, a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2 % lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20 % DX was mixed with 0.5 ml of 2 % lidocaine and the injection was repeated monthly for 3 months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at 1, 2, and 6 months after the treatment.
Results Mean age (STD) was 63.6 (9.7) years, and mean (STD) visual analog scale (VAS) was 6 (2). The two groups were comparable at 2 months, but significantly different at 1 month, with better results for corticosteroid, and at 6 months with apparently more favorable outcome for DX [mean difference (95 % CI) in VAS = 1.1 (0.2, 2.0), $p = 0.02$]. After 6 months of treatment, both DX and corticosteroid injection increased functional level, but DX seemed to be more effective [mean difference (95 % CI) in total function score = 1.0 (0.2, 1.8), $p = 0.01$].
Discussion For the long term, DX seems to be more advantageous, while the two treatments were comparable in the short term. Because of the satisfactory pain relief and restoring of function, we would prefer DX prolotherapy for the treatment of patients with OA.
Level of evidence Therapeutic studies—investigating the results of treatment; level I.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease [1, 2]. The prevalence of symptomatic hand OA in people over 70 years of age has been estimated as 13.4 % for men and 26.2 % for women [3]. OA is more frequent in older age groups, leading to considerable disability with a burden on health services and on the economy [2]. Inconsistent evidence has been reported for an association between radiographic OA and hand disability [2]. Osteoarthritis Research Society International suggested three sets of clinical outcome measure including patient-reported pain, physical function and patient global assessment, in order to assess treatments in hand OA [4].

Corticosteroid injection is helpful in the treatment of the disease, but some patients gain only short-term benefits [5–7]. Prolotherapy has been used as a treatment of musculoskeletal pain with various etiologies [8–10]. It has been suggested that prolotherapy induces little inflammation and stimulates endogenous repair especially by prompting release of growth factors [5, 11–13]. Dextrose (DX) is an agent commonly used for prolotherapy [5, 14–16].

This trial has been registered at the Iranian Registry of Clinical Trials (IRCT) website http://www.irct.ir/, a WHO Primary Register set-up, with registration code: Irct ID: IRCT201011025088N1.

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There are researchers who believe that prolotherapy is still investigational [17]. Some studies suggested advantages [11, 13–16, 18–23] and others, no effect [9, 17, 24–26]. In a systematic review of randomized controlled trials researchers declared that, when compared with hip and knee OA, there are few published randomized controlled trials in hand OA and those trials are of poor quality, and lack consistent definitions and standardized outcome assessments. The methods used for randomization, blinding, and allocation concealment are rarely described [27]. Therefore, comparisons of the treatments over the long term are required [6], using less expensive and more practical methods [28].

In this prospective study the advantages of prolotherapy in the treatment of the first carpometacarpal joint (CMC1) OA were compared with those of corticosteroid local injection. The hypothesis for this study was that prolotherapy treatment would be more effective than cortisone injection for treatment of CMC OA. We conducted a randomized clinical trial to determine the treatment that improves symptoms and restores function, more effectively. To assess the treatments we used both patient and non-patient reported outcomes.

Materials (patients) and methods

Design and setting

We performed a randomized controlled trial study. The study was conducted from March 2010 to March 2011 in an outpatient clinic of physical medicine and rehabilitation at a large referral practice and academic center.

Participants

We recruited patients with OA of CMC1 who came to the clinic, or were referred by primary care physicians. At the first hospital visit patients were screened for eligibility. Of 112 potential eligible patients 12 were excluded, 4 refused to participate, and of the remaining 96 patients, 60 were selected randomly as our analytic sample; 30 for the group prolotherapy, and 30 for the group corticosteroid (Fig. 1).

Eligibility criteria

Patients were included if they were more than 40 years of age, had history of pain in CMC1 for at least 3 months and pain with the intensity of more than 30 in a 100-mm visual analog scale (VAS) at the baseline visit, and if they were motivated to receive injection. They were also required to have evidence of OA in their CMC1 based on radiographic criteria including: moderate osteophytosis, moderate joint space narrowing, or mild osteophytosis plus mild joint space narrowing, or subchondral sclerosis, or subluxation. According to the Eaton classification, included participants were beyond stage one. A board-certified radiologist reviewed the X-rays and an assistant professor of physical medicine examined the patients.

Exclusion criteria were a history of fracture or other hand pathologies such as tendinitis, inflammatory diseases like rheumatoid arthritis, local infections, and metabolic bone disease within 6 months before the study. Participants were excluded if they had diabetes, blood coagulation disorders, neuropathy, corticosteroid injection during the last 3 months, and contraindications to steroid injection. Pregnant or breast feeding mothers, participants who were taking NSAIDs or wearing a brace at the time of the study, and patients with a history of injection into their CMC1 within the last 6 months were not included in the study.

Randomization

In participants with bilateral OA of the CMC1 we selected the hand with more severe symptoms, and if the severities were equal, we chose one hand randomly. Treatment allocation was performed at the baseline assessment. A computer-generated randomization list of 60 items in blocks of variable sizes, unknown to the investigators involved in recruiting patients, was prepared. Therefore, we had two groups of 30 participants each; group DX and local corticosteroid (LC). Immediately following the allocation, the patients received the assigned treatment.

Allocation concealment

We used sequentially numbered sealed envelopes containing cards with group assignments that were prepared in a trial coordinating center, and were marked with the patients' sequential numbers. When a patient was enrolled and written informed consent obtained, the study nurse opened the envelope and prepared the injection according to the card and then signed date, name and sequential number on a list.

Blinding

The clinical assessor was blinded to the baseline evaluations and to the administered treatments. We gave some information about the medications used in the study to the participants, but they were blinded to their group allocation. The study radiologist was unaware of the study question.

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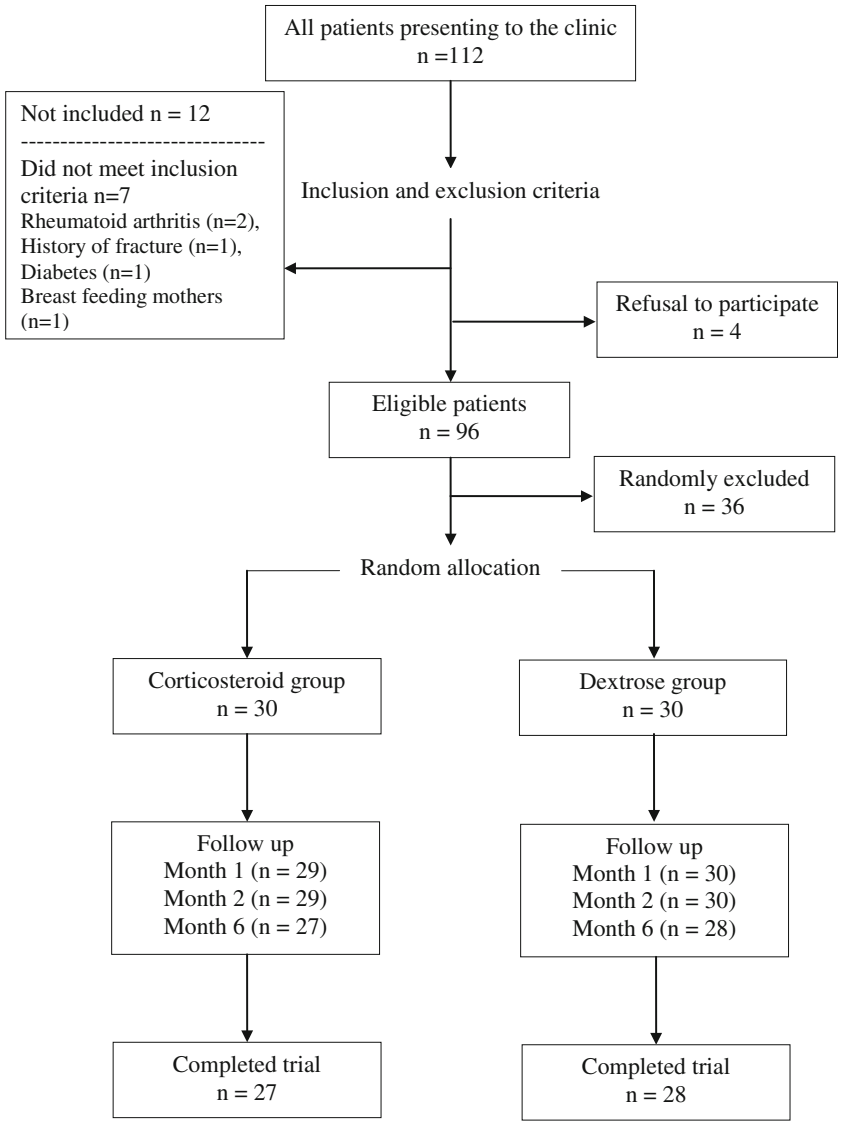

Fig. 1 Flow of participants through each stage of the randomized trial

Protocols and procedures

Diagnosis

At the baseline visit, history was recorded by interview and a self-administered questionnaire pertaining to demographics, duration of the symptoms and comorbid conditions. Also, a careful history of medication use including analgesics was taken. In addition, the recruitment questionnaire asked about any previous procedure, consultation with a physician, and active treatment.

Hand examinations for the baseline visit included observation of deformity, sensory, and motor examinations, and muscle testing for atrophy and weakness. The examinations also consisted of the strength of lateral pinch, hand function in various tasks of daily activity measured with the Health Assessment Questionnaire Disability Index (HAQ-DI), and pressure pain threshold [29]. Appropriate laboratory tests were ordered for the assessment of comorbid conditions. Radiographs of the hand were obtained at the baseline visit for all participants.

Outcome measures

As the primary outcome, a visual analog scale (VAS) was used to measure subjective pain intensity. Participants recorded their self-scored pain perception by corresponding it to a 100-mm line ranging from 0 (no pain) to 9 (worst pain). We measured the intensity of tenderness by means of Fischer's pressure algometer to measure pain threshold to pressure. We applied 40 N/cm^2 for all participants.

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Some secondary outcomes were assessed in our study, as well. Pain on joint movement was measured with VAS, too. Hand function was evaluated using the self-administered questionnaire HAQ-DI for the ability to perform three daily activities including eating, gripping, and dressing. Patients stated their levels of functionality by matching them to the numbers: 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), and 3 (unable to do) within the last week. The questionnaire was also used to assess improvement in the functional status of patients to evaluate the advantages of the treatments. We evaluated the strength of lateral pinch grip objectively in pounds (lb), by baseline hydraulic pinch gauge. Lateral pinch was measured as pad to side between the thumb and index fingers at the maximum strength. All the outcomes were evaluated at the baseline visit and at 1, 2, and 6 months after the third injection.

Study interventions

The chief resident of physical medicine and rehabilitation administered the injections for the two groups. In the group LC, 2 monthly placebo injections of 1 ml 0.9 % saline were administered (for masking) followed by a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2 % lidocaine in the 3rd month. For the group DX, 0.5 ml of 20 % DX mixed with 0.5 ml of 2 % lidocaine was injected. Like previous studies, the procedure was repeated monthly for 3 months. Therefore, participants in the group LC got their treatment in the third session, while individuals in the group DX received three doses of DX solution. A 25-gauge needle was inserted toward the ulnar side of the extensor pollicis brevis and just proximal to the base of the first metacarpal in the snuffbox. After aspiration, 1 cc of the solutions was injected into intra and peri-articular locations. We used lidocaine to relieve pain at the site of injection. All the patients were asked to return gradually to normal activities but to avoid pain-provoking physical stresses, especially within the first 48 h after injection. Participants were also instructed not to use a brace, physiotherapy, and analgesic medications.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Army University of Medical Sciences. The rationale of the study and the possible side effects were explained to all participants. All patients signed written consents and they were referred for appropriate treatment, if needed. Patients were informed that they were free to withdraw from the study at any time. Participants did not pay for the treatment.

Sample size

We estimated a sample size of 30 participants in each group based on the primary outcome measure of the severity of pain on pressure, ability to detect a difference of 30 %, a power of 80 %, and a two-tailed p value of 0.05 as statistically significant.

Statistical analyses

Data was presented as mean (standard deviation), for continuous variables, and as numbers and proportions for categorical variables. For non-normal data, the median value and inter-quartile range was reported. Data were tested for normality using the Kolmogorov–Smirnov test with Lilliefors significance correction. In case of normal distribution, an independent samples t-test was used for between group comparisons, otherwise, the Mann–Whitney U test was performed. Within-group analyses were carried out by the use of a paired t-test, or its nonparametric equivalent; Wilcoxon rank-sum test. The Kaplan–Meier survival analysis with a log-rank test was used to compare the two groups longitudinally, with regard to the event of 30 % decrease in VAS. Data was analyzed with a statistical software package (SPSS for Windows, version 13, SPSS, Inc., Chicago, IL, USA). A p value of <0.05 was considered significant, and the power of statistical tests was set at 80 %.

Results

The analytic sample was composed of 60 participants (60 hands). Mean age (STD) was 63.6 (9.7) with the range of 42–83 years. Of these 60 patients, 44 (73 %) were female. Participants had various occupations from low to high physical levels of activity. Mean (STD) of VAS was 6 (2), and 4.7 (1.2) for tenderness and pain on movement, respectively. The modes of scores for dressing, gripping, and eating were 1, 2, and 1, respectively. Mean (STD) of the strength of lateral pinching was 10 (3.8). For 53 % of participants the duration of their symptoms was more than 10 months. In 25 (42 %) patients, the dominant hand was affected. The groups were comparable except for pinching (Table 1).

Within-group analyses showed that in both groups, after 6 months of treatment, differences between the outcome scores were significant (Table 2). Both LC and DX groups showed improvements in pain (47 % vs 76 % decrease, respectively), strength of pinching (9 % vs 24 % increase), and function (41 % vs 65 % decrease in total score). Also, Table 3 demonstrates the results of between-group analyses at each time point of the follow-up.

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Table 1 Baseline characteristics of LC and DX groups

Characteristic	Study groups		*p* value
	LC	DX	
Women (%)	21 (70)	23 (77)	0.77
Age (year), mean (STD)	63.3 (10.1)	63.9 (9.4)	0.84
Duration of the symptoms (months), mean (STD)	11.3 (9.3)	10.7 (7.7)	0.81
Pain on pressure (VAS), mean (STD)	6.4 (1.8)	6.7 (1.7)	0.56
Pain on movement (VAS), mean (STD)	4.5 (1.6)	5.0 (2.1)	0.29
Pinching, mean (STD)	11.6 (3.6)	9.6 (3.4)	0.03
Dominant hand (%)	12 (40)	13 (43)	1.00
Hand function, mean (STD)			
Dressing	1.2 (0.5)	1.1 (0.7)	0.69
Gripping	2.0 (0.6)	2.2 (0.8)	0.28
Eating	1.2 (0.6)	1.2 (0.6)	0.67
Total	4.37 (1.4)	4.6 (1.8)	0.63

Table 2 Within-group comparisons of the secondary outcomes; baseline vs 6 months after the treatments

	Mean (STD) at 6 months	Mean difference (95 % CI)	*p* value
LC			
Pain on movement (VAS)	2.4 (1.8)	0.5 (0.3, 0.7)	<0.001
Pinching	12.7 (4.3)	−0.9 (−1.5, −0.5)	0.001
Hand function (total score)	2.6 (1.5)	1.5 (1.0,1.9)	<0.001
DX			
Pain on movement (VAS)	1.2 (1.6)	3.8 (2.9, 4.8)	<0.001
Pinching	11.9 (3.4)	−2.6 (−3.9, −1.2)	<0.001
Hand function (total score)	1.6 (1.3)	2.8 (2.2, 3.5)	<0.001

Table 3 Between-group comparisons of the secondary outcomes at 1, 2, and 6 months after the treatments (LC–DX)

	Follow-up stages		
	1 month	2 months	6 months
Pain on movement (VAS)			
Mean difference (95 % CI)	−0.7 (−1.8, 0.2)	1.0 (0.1, 2.0)	1.1 (0.2, 2.0)
p value	0.14	0.02	0.02
Pinching			
Mean difference (95 % CI)	2.9 (0.9, 4.9)	1.1 (−0.8, 3.1)	0.8 (−1.3, 2.9)
p value	0.005	0.25	0.45
Hand function (total score)			
Mean difference (95 % CI)	0.5 (−1.3, 0.2)	1.0 (0.2, 1.9)	1.0 (0.2, 1.8)
p value	0.15	0.01	0.01

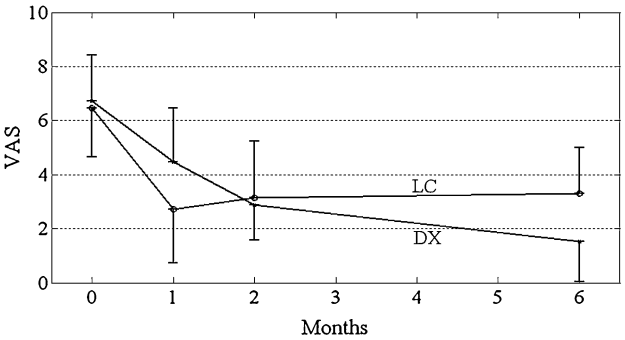

Fig. 2 Changes in mean VAS for severity of pain on pressure for the two treatment groups. *Vertical bars* represent standard deviations

In the first month, it appears that the pain score decreased more with LC rather than DX, but the difference was not significant. Pinching strength was different, with a more favorable result in the LC group. The mean total function scores showed better outcomes, though non-significant, with DX. In the 2nd month, the pain score was significantly more with LC. The difference in pinch strength declined and became non-significant, and hand function improved significantly in the group DX compared to LC. After 6 months, pain on movement had diminished more significantly in the group DX; difference in pinch strength was smaller and still non-significant; and hand function was significantly better with DX.

At the baseline, mean score for pain on pressure was 6.5 in the LC group, and 6.7 in the DX group. The distributions of pain on pressure were skewed to the left in both groups with skewnesses of −0.34 and −0.44 for LC and DX, respectively. Median (interquartile range) was 7 (3) for both groups. The data was not normally distributed for pain on pressure in the DX group [$D(30) = 0.17$, $p = 0.03$], while in the group LC, the data was normally distributed [$D(30) = 0.15$, $p = 0.08$]. The Mann–Whitney test showed that the two groups were comparable at the baseline ($p = 0.56$), and at 2 months ($p = 0.88$), but significantly different at 1 month, with a better result for group LC ($p = 0.001$), and at 6 months with apparently more favorable outcome for group DX ($p = 0.001$) (Fig. 2). Patients were evaluated at the baseline and at three time points during the study. The curves for severity of pain on pressure crossed (Fig. 2), so we did not perform the Kaplan–Meier analysis or log-rank test. The participants did not report any significant side effects. However, three patients experienced transient increases in pain at the site

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of injection which subsided within several days. There was no sign of infection or any other complication at the site of injections.

Discussion

We found good evidence to support the use of DX over LC injection for the treatment of OA of CMC1 in terms of pain relief and function restoration. After 6 months of treatment, both DX and LC injection had diminished the severity of symptoms, and increased function, but DX seemed to be more effective. In the short term, LC abated the symptoms rapidly, but after a while the manifestations partially recurred. In the DX group the symptoms reduced more slowly and constantly, and the treatment effect remained more steady. The difference was remarkable at 6th months when symptoms abated and functions improved more desirably in DX. Our results showed that LC, though initially successful, was not as effective as DX.

Our findings are consistent with the results of some previous studies. Follow-up studies have shown that LC injection has reduced pain sensation and increased function compared with some other treatments for a short time.

In a prospective case series study, the efficacy of intra-articular corticosteroid injections for OA of the CMC1 was evaluated [6]. A total of 0.25 ml of methylprednisolone acetate was injected into the CMC1 in 25 patients, who were followed for 1 year. A significant improvement in the VAS for pain was noted at 1 month. That study demonstrated an improvement in daily activities, and only minor side effects in two participants, although a significant long-term benefit was not observed.

In a systematic review with meta-analysis [30], intra-articular steroid injections for painful knees were evaluated. It was concluded that the beneficial effect could last for 3–4 weeks. Similarly, our study showed that participants in the LC group experienced a prominent symptomatic relief 1 month after treatment. However, the improvement was not so noticeable thereafter.

Previous studies have demonstrated several advantages of prolotherapy. In a randomized double-blind placebo-controlled trial the effects of DX prolotherapy on knee OA were investigated [15]. Participants (38 knees) with 6 months or more of pain in the knee were included. Three bimonthly injections of 9 cc of either 10 % DX and 0.075 % lidocaine or an identical control solution without the 10 % DX were administered. The DX-treated joints then received 3 further bimonthly injections of 10 % DX. By 12 months (6 injections) the DX-treated knees improved in pain (44 % decrease), swelling complaints (63 % decrease), knee buckling frequency (85 % decrease), and in flexion range (14° increase). The researchers reported that prolotherapy injection with 10 % DX resulted in clinically and statistically significant improvements in knee OA. The results had some similarities with those of our research, in the favorable outcomes of prolotherapy for OA.

In a randomized controlled trial researchers have evaluated the clinical benefit of DX prolotherapy in osteoarthritic finger joints [14]. Distal interphalangeal (DIP), proximal interphalangeal, and trapeziometacarpal joints were studied. Thirteen patients received active treatment, and 14 served as controls. A preparation of 0.5 ml of either 10 % DX and 0.075 % Xylocaine (active solution) or 0.075 % Xylocaine (control solution) was injected into medial and lateral aspects of each affected joint at 0, 2, and 4 months with assessment at 6 months after the first injection. Pain with movement of fingers improved significantly more in the DX group (42 % vs 15 %). It was concluded that DX prolotherapy is clinically effective and safe in the treatment of osteoarthritic finger joints. This result is consistent with the findings of our study for the efficacy of DX 10 % prolotherapy in hand OA, although we compared two treatment protocols (DX vs corticosteroid), as well.

In a study, 24 individuals with refractory lateral epicondylosis participated in a double-blind randomized controlled trial [19]. Prolotherapy participants received injections of a solution made from 5 % sodium morrhuate, 50 % DX, 4 % lidocaine, 0.5 % sensorcaine and normal saline. Controls received injections of 0.9 % saline. Three 0.5-ml injections were administered at baseline and 4 and 8 weeks. Prolotherapy subjects reported greater reduction in pain scores. At 16 weeks, these differences were significant compared to baseline scores within and among groups ($p < 0.001$), and the study reported an effective decrease in elbow pain, and improved strength testing. The follow-up period of 52 weeks for that study especially confirmed the efficacy of long-term prolotherapy.

Our study was sufficiently large and prolonged to detect clinically important differences. Statistical analyses were straightforward, and missing data was not frequent. We used symptomatic improvement as the surrogate of treatment effect, instead of serially taken radiographs. We did not have constant access to a sonographist to perform the injections under the guide of sono; however, we used lidocaine to relieve pain at the site of injection as a relative guide.

Both LC and DX can relieve pain and suppress inflammatory processes. Furthermore, DX has been suggested to strengthen soft tissue too. There are some reports indicating improvement in ligament laxity after DX prolotherapy. Also, it has been suggested that pain reduction in injected joints might be a result of tissue stabilization [5–14]. Preliminary blinded radiographic readings in one study

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demonstrated improvement in several measures of OA severity [15]. There is no important difference between DX and LC regarding costs. The side-effects of LC have been sufficiently reported in the literature, while little is known about complications of DX prolotherapy. Further research with a large sample size is needed to compare possible complications of LC vs DX injections in the management of OA.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. van Saase JLS, van Romunde LKR, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis. 1989;48:271–80.
2. Kloppenburg M. Hand osteoarthritis—an increasing need for treatment and rehabilitation. Curr Opin Rheumatol. 2007;19:179–83.
3. Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliubadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among elderly. Am J Epidemiol. 2002;156:1021–7.
4. Maheu E, Altman RD, Bloch DA, Doherty M, Hochberg M, Mannonia A, Punzi L, Specto T, Verbruggen G. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International. Osteoarthr Cartil. 2006;14:303–12.
5. Cusi M, Saunders J, Hungerford B, Wisbey-Roth T, Lucas P, Wilson S. The use of prolotherapy in the sacro-iliac joint. Br J Sports Med. 2010;44:100–4.
6. Joshi R. Intra-articular corticosteroid injection for first carpo-metacarpal osteoarthritis. J Rheumatol. 2005;32:1305–6.
7. Toker S, Kilinçoğlu V, Aksakalli E, Gülcan E, Ozkan K. Short-term results of treatment of tennis elbow with anti-inflammatory drugs alone or in combination with local injection of a cortico-steroid and anesthetic mixture. Acta Orthop Traumatol Turc. 2008;42:184–7.
8. Dagenais S, Haldeman S, Wooley JR. Intraligamentous injection of sclerosing solution (prolotherapy) for spinal pain: a critical review of the literature. Spine J. 2005;5:310–28.
9. Dagenais S, Yelland MJ, DelMar C, Schoene ML. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. 2007;18:CD004059.
10. Rabago D, Best TM, Beamsley M, Pattersn J. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sport Med. 2005;15:376–80.
11. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby RJ. Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res. 2008;26:816–23.
12. Schmidt H. Effect of growth factors on proliferation of fibroblasts from the medical collateral and anterior cruciate ligaments. J Orthop Res. 1995;13:184–90.
13. Schwartz R. Prolotherapy: a literature review and retrospective study. J Neurol Orthop Med Surg. 1991;12:220–3.
14. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. J Altern Complement Med. 2000;6:311–20.
15. Reeves K, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med. 2000;6:68–74.
16. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. Altern Ther Health Med. 2003;9:58–62.
17. Dagenais S, Ogunseitan O, Haldeman S, Wooley JR, Newcomb RL. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil. 2006;87:909–13.
18. Ongley MJ, Klein RG, Dorman TA, Eek BC, Hubert LJ. A new approach to the treatment of chronic low back pain. Lancet. 1987;2:143–6.
19. Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clin J Sport Med. 2008;18:248–54.
20. Watson JD, Shay BL. Treatment of chronic low-back pain: a 1-year or greater follow-up. J Altern Complement Med. 2010;16:951–8.
21. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J Sports Med. 2011;45:421–8.
22. Klein RG, Eek BC, DeLong WB, Mooney V. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. J Spinal Disord. 1993;6:23–33.
23. Kim WM, Lee HG, Jeong CW, Kim CM, Yoon MH. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med. 2010;16:1285–90.
24. Chou R, Atlas SJ, Stanos SP, Van zundert J, Vanelderen P, Kessels AG. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine. 2009;34:1078–93.
25. Yelland MJ, Glasziou PP, Bogduk N, Kidd R. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine. 2004;29:9–16.
26. Dagenais S, Mayer J, Haldeman S, Borg-stein Y. Evidence-informed management of chronic low back pain with prolotherapy. Spine J. 2008;8:203–12.
27. Towheed TE. Systematic review of therapies for osteoarthritis of the hand. Osteoarthr Cartil. 2005;13:455–62.
28. Kjeken I, Dagfinrud H, Slatkowsky-Christensen B, Mowinckel P, Uhlig T, Kuien TK, Finset A. Activity limitations and participation restrictions in women and hand osteoarthritis: patients' descriptions, and associations between dimensions of functioning. Ann Rheum Dis. 2005;64:1633–8.
29. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire (HAQ): a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30:167–78.
30. Godwin M, Dawes M. Intra-articular steroid injections for painful knee: systematic review with meta-analysis. Can Fam Physician. 2004;50:241–8.

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