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Original Article

A comparative study on the effects of dextrose prolotherapy and local steroid injection in patients with lateral epicondylitis: A randomized controlled trial

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Abstract

Background

Lateral epicondylitis (LE) is the most common condition of elbow pain. Multiple intralesional steroid injections help in the treatment. Prolotherapy is a traditional injection method recently categorized as regenerative treatment. However, there is scarcity of literature that compares its effectiveness with steroids.

Objective

The aim was to compare the effectiveness of dextrose prolotherapy (DP) against local steroid injection in patients with LE in relieving pain and improving dysfunction.

Participants and methods

This parallel, randomized controlled trial was conducted at Outpatient Department, National Institute for Locomotor Disabilities (Divyangjan), (erstwhile National Institute for the Orthopaedically Handicapped) Kolkata, from January 2016 to January 2017. Patients with the clinical diagnosis of LE (in clinical stages 2, 3, and 4) were allocated to receive either DP (group A) or local steroid injection (group B). A total of 34 participants aged between 18 and 60 years who had symptoms for greater than or equal to 4 weeks was included. Injections were given to each patient at 0, 4, and 8 weeks. Data were collected at baseline and followed up at the fourth, eighth, and 16th weeks. The two interventions' differential response was recorded in terms of pain [visual analog scale (VAS)], upper-extremity activities (DASH; disabilities of the arm, shoulder and hand scale), and the pain-free grip strength (PFGS).

Results

Both groups A and B showed significant improvement ($P < 0.05$) in VAS, DASH, and PFGS at follow-ups compared with baseline. Compared with group B, at 4 weeks, group A had no statistically significant differences in the VAS (53.6 ± 12.6 vs 51.3 ± 15.5, $P = 0.65$), DASH score (26.2 ± 14.6 vs 26.7 ± 15.6, $P = 0.93$), and PFGS (16.3 ± 8.7 vs 12.3 ± 5.4, $P = 0.14$).

Compared with group B, at 8 weeks, no statistically significant differences in the VAS ($n = 15$, difference of mean 0.4, 95% confidence interval [−7.4 to 8.2], $P = 0.9$), DASH ($n = 15$, 3.5 [−5.2 to 12.2], $P = 0.4$), and PFGS ($n = 15$, 4.7 [−0.8 to 10.2], $P = 0.1$) were noted between two groups. However, at 16 weeks, compared with group B, group A patients showed significant better improvement in VAS ($n = 15$, 14.0 [7.0–20.9], $P = 0.0001$) and PFGS ($n = 15$, 8.4 [2.3–14.5], $P = 0.009$) but not in DASH ($n = 15$, 8.4 [2.3–14.5], $P = 0.4$).

Conclusions

DP showed superiority in reducing LE pain and improving the grip strength as compared with local steroid injection. However, prolotherapy was associated with increased pain around the injection site in the first 48 h and transient weakness of wrist extensors (about 10 min) because of local spread of lignocaine in the common extensor-origin muscles, which was conservatively managed.

Keywords: Functional impairment, lateral epicondylitis, prolotherapy, steroid injection

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Introduction

Lateral epicondylitis (LE), also called tennis elbow syndrome, is known to be the most common condition of elbow pain with a prevalence of 1–2% among the normal population aged 30–65 years, and up to 40% among certain subgroups such as professional tennis players [1–4]. Highly repetitive activities might be the most important cause of LE [5]. LE can affect the daily activities of individuals, and in severe cases, it can impose a relatively high financial burden on the sufferers [1,3]. Chronic LE was considered in cases lasting more than 3 months as opposed to early or subacute LE [5]. There are several nonsurgical options for the treatment, but the current literature has not provided any conclusive evidence regarding the nonsurgical methods [2].

Nonsurgical therapies include anti-inflammatory drugs, prefabricated splints, eccentric forearm–dorsiflexors exercise, injections, and last, the physical agent modalities such as ultrasound, extracorporeal shockwave therapy, and low-level LASER [2,6]. There are multiple types of intralesional injections, including autologous blood, platelet-rich plasma, botulinum toxin, ozone-oxygen solution, hyaluronic acid, dextrose prolotherapy (DP), and steroid, that may aid in the treatment. The last two options have been conventionally more available and are the main issue of this investigation [1,7–10].

Prolotherapy is a traditional injection method that has been recently categorized as a regenerative treatment. Conventionally, hypertonic dextrose (10–20%) has been used in prolotherapy. It can result in a stimulated local inflammation and helps the restoration of the injured tissue. Based on previous research, it seems that prolotherapy can stimulate the healing process, reduce pain, and improve function in chronic musculoskeletal problems such as LE. However, the exact mechanism of action is not yet fully understood [11–14]. The strength of existing evidence in favor of prolotherapy is considered as level-B recommendations [8,15].

On the other hand, steroid injection has been known as the most rapid treatment for early epicondylitis. However, the present literature is not enough to support its effectiveness in chronic cases. Also, in the medical fraternity, there is no consensus that which treatment modality is best and when to use. There are few literatures available on the effectiveness of DP injections as a treatment option for the LE. Very few studies have evaluated the effectiveness of DP injections as a treatment modality of LE, therefore this research was undertaken. In fact, although it was beneficial for short-term pain relief of acute conditions, the mid-term and long-term follow-up did not support the use of steroids [6,16,17]. This study aimed to evaluate the efficacy of steroid injection versus DP in patients with LE of clinical stages 2, 3, and 4. The primary objectives were to assess pain scores and functional disability.

Participants and methods

Study setting

Outpatient Department, Department of Physical Medicine and Rehabilitation, National Institute for Locomotor Disabilities (Divyangjan), (erstwhile National Institute for the Orthopaedically Handicapped) Kolkata-700090.

Study design

The study was designed as a randomized controlled trial with a 1 : 1 allocation ratio to receive either DP (group A) or local steroid injection (group B).

Study participants

Eighty-nine patients with the clinical diagnosis of LE who presented to the Department of Physical Medicine and Rehabilitation in a tertiary care center from December 2015 to June 2016 were evaluated.

Inclusion criteria

Participants aged 18–60 years who had symptoms for 4 weeks or longer, with pain in visual analog scale (VAS) greater than 40%, were included. Both newly diagnosed cases of LE and those who had failed a course of conservative management (NSAIDs, exercise therapy) of any duration were included. Patients with stages 2, 3, and 4, that is, chronic cases, were included.

Exclusion criteria

Stage 1 cases were excluded because it is acute. Those with a history of allergy to steroid injections, bleeding disorders, elbow-joint effusion, rheumatologic conditions, previous treatment with prolotherapy injection or steroid injection for LE, local infection at the site of injection, uncontrolled diabetes or other comorbid conditions, pregnant or lactating mothers, and psychiatric or cognitive problems (which may hamper the outcome evaluation) were also excluded from the study.

Ethical considerations

The Institutional Ethical Committee approved the study (IEC/1610/R&D/08/NIOH/16). Privacy and confidentiality of all the patients were maintained. A duly informed written consent was taken from all the patients.

Sample size

Considering the absolute effect size of 76% from the previous study14, the power of 86%, and a two-tailed α of 0.05, a sample size of 15 in each group was calculated. Considering the drop-out rate of 10%, the total sample size was estimated to be 34.

Randomization and blinding

Among the mentioned population, eligible participants were randomly assigned into two categories using computer-based randomization software and envelope-concealment method. The recruitment, outcome measurement, and statistical analysis were done by investigators. Neither the patient nor the investigator was blinded to the intervention.

The diagnosis was made clinically based on pain localized to the elbow's lateral epicondyle, typically exacerbated by

contraction of forearm extensors with repetitive activities, by the primary investigator (resident doctor) under the supervision of the senior consultant with an experience of over 15 years. A plain radiograph of elbow anterior–posterior and lateral view, routine blood investigation (complete blood count, erythrocyte-sedimentation rate, and blood sugar fasting and postprandial) was obtained.

Intervention

Before injection, a skin hypersensitivity test was performed. In group A (DP group), 5 ml of 12.5% dextrose injection was used (by mixing 2.5 ml of 25% dextrose and 2.5 ml of 2% lignocaine). The injection was given to the lateral epicondyle region according to the Barbotage approach[9] using a 24-gauge 1.5-inch needle. In the DP group, three injections were administered at baseline, fourth week, and eighth week in all the patients.

In group B (steroid group), 2 ml of 20 mg of local steroid injection was prepared (by mixing 1 ml of 20 mg of methylprednisolone acetate and 1 ml of 2% lignocaine). The injection was administered using a 24-gauge 1.5-inch needle with a standard blinded approach [10]. In the steroid group, one injection was given at baseline in all the patients and repeated once in the 4th week only if the pain alleviation was not relieved, that is, VAS greater than or equal to 40.

After each injection, patients were asked to use ice massage for 5–10 min on the injection site, and tablet acetaminophen 500 mg was advised as and when on a required basis. The trial was stopped if the patient had pain scores in the range of 10 even after the administration of the intervention at the second follow-up or beyond, or there was a severe allergic reaction to the treatment.

Follow-up interventions

Patients in both the groups were taught to perform wrist extensor stretching exercises at home after taking rest for 2 days:

(1) Stretching: 10 s per set ×3 sets thrice a day ×3 days.
(2) Stretching of wrist extensors: 10 s per set ×3 sets thrice a day+eccentric strengthening of wrist extensors: 10 repetitions per set×thrice a day ×1 week.
(3) Stretching of wrist extensors: 10 s per set ×3 sets thrice a day+eccentric strengthening of wrist extensors: 10 repetitions per set×thrice a day.
(4) Isometric strengthening of shoulder internal rotators and external rotators: 10 repetitions per set to continue.

Patients were instructed not to take any NSAIDs from 1 week before to 16 weeks after the first injection. All patients were advised of therapeutic lifestyle changes. Eventually, participants were instructed how to wear their splint (tennis elbow band) correctly and to do gentle stretching exercises of the common extensors regularly for three sessions per week. After 2 weeks, eccentric-loaded exercises were started twice a day. Follow-up of the patients was done at 4, 8, and 16 weeks.

Outcome measure

A VAS 0–100 was used for assessing pain intensity and where 0 is 'no pain' and 100 is 'extreme pain'. The summary intraclass correlation coefficients (ICC) for all paired VAS scores have been estimated to be 0.97 [95% confidence interval = 0.96–0.98] with validity from the last 18 years for assessing acute pain [11].

Disabilities of the arm, shoulder and hand scale (DASH) was used to determine the patient's ability to perform certain upper-extremity activities. This 30-item questionnaire is a self-report questionnaire that patients can rate and interference with daily life on a five-point Likert scale. The reliability of the DASH is excellent (ICC 0.97) with strong internal consistency (Cronbach's α 0.97) [12].

Pain-free grip strength (PFGS) was assessed. This test is used for measuring the amount of force that is generated by the patient on the onset of pain. In the absence of pain, the test result is considered to be the maximum grip strength. PFGS was measured using Jamar Hydraulic Hand Dynamometer13 (Model 081028935), 200 lb. Patients were asked to grip the squeezer for 3–5 s with a 60-second gap between grips where the elbow was kept extended while squeezing. Three consecutive grip strengths were recorded, and the mean value (in kilograms) was used for analysis. High levels of test–retest reliability (ICC $\geq$ 0.91) exist for pain-free grip-strength testing.

The outcome variables were recorded at baseline and at the end of 4, 8, and 16 weeks.

Statistical analysis

Statistical analysis was performed with the help of Epi Info (TM) 3.5.3, which which was developed by Center for Disease Control and Prevention (CDC), Atlanta, Georgia (US). Basic cross-tabulation and frequency distributions were prepared using this software. A χ^2-test was used to test the association between different study variables under study. Corrected χ^2-test was used if any one of cell frequency was found less than 5 in the bivariate frequency distribution. The test of proportion (*Z*-test) was used to test the significant difference between the two proportions. The *t*-test was used to test the significant difference between mean. Also, one-way analysis of variance (ANOVA) followed by post-hoc Tukey's test was performed with the help of critical difference (CD) or least significant difference at 5% and 1% level of significance to compare the mean values. *P* value less than 0.05 was considered statistically significant.

Results

Eighty-nine participants who met the initial inclusion criteria were approached for the study proposal, among which 34 patients were found to be eligible, and 55 patients were excluded. Out of the 34 patients enrolled in the study, a total of 30 completed a full 16-week follow-up, 15 in each

group. A total of four patients, two in each group, were lost to follow-up and were excluded from the statistical analysis, as depicted in the CONSORT flow diagram (Fig. 1).

The mean age of the participants was 42.38 ± 9.23 years, with a range of 22–63 years. Seventeen were females, and 17 were males. In 28 patients (82.35%), the right elbow was affected, while in six (17.65%), the left-sided elbow was affected. The average reported duration of symptoms was 32 ± 27.3 weeks, with a range of 4–104 weeks. At randomization, both groups' baseline demographic and outcome variables were comparable, as depicted in Table 1.

One-way ANOVA showed significant improvement in pain intensity in terms of VAS scores within group A and group B at different time points compared with baseline ($P < 0.0001$). Also, as per CD, significant improvement was observed in mean VAS at different time points compared with baseline ($P < 0.001$).

There was no statistically significant difference observed between the VAS score of group A and group B at 4 and 8 weeks of follow-up ($P > 0.05$). However, at the 16th week, VAS score of group A patients was significantly lower than group B ($P = 0.0003$), as depicted in Table 2.

One-way ANOVA showed significant improvement in pain intensity in terms of DASH scores within group A ($P < 0.0001$) and group B ($P = 0.004$) at different time points compared with baseline. Also, as per CD, significant improvement was observed in the mean DASH score at different time points compared with baseline ($P < 0.001$).

There was no statistically significant difference observed between the DASH score of group A and group B at 4, 8, and 16 weeks of follow-up ($P > 0.05$), as depicted in Table 2.

There was a significant improvement in the grip strength in terms of PFGS value within group A ($P < 0.00001$) and group B ($P = 0.008$) at different time points compared with baseline.

The PFGS value of group A patients was higher at 4 weeks and 8 weeks than that of group B patients, but it was not significant ($P > 0.05$). At the 16th week, the mean PFGS of group A was significantly higher than that of group B patients ($P = 0.009$), as depicted in Table 2.

All the patients in the prolotherapy group reported increased pain around the injection site in the first 48 h, for which oral acetaminophen tablets were given on an emergency basis, and pain relief was achieved within 24 h of onset. At five instances, transient weakness of wrist extensors (about 10 min) was observed after the injection in the DP group, a possible explanation being the local spread of lignocaine in the common extensor-origin muscles.

Discussion

This investigation showed that both corticosteroid injection and DP efficiently improved pain and function in patients with chronic LE. In the DP group, this improvement was significantly more after 4 months of follow-up than in the steroid-only group. This finding proved that DP had better and longer effects in treating chronic tennis elbow; however, the impact of exercise and splinting as the basic treatment should not be ignored in the improvement of patients. Prior research has achieved a level 1B of evidence for the efficacy of prolotherapy [9,18]. Among the few studies assessing prolotherapy effectiveness in tennis elbow, we compare our results with some of the most important ones [3,19,20].

Primarily, in 2008, Scarpone and colleagues evaluated the efficacy of prolotherapy (dextrose 11%) in refractory tennis

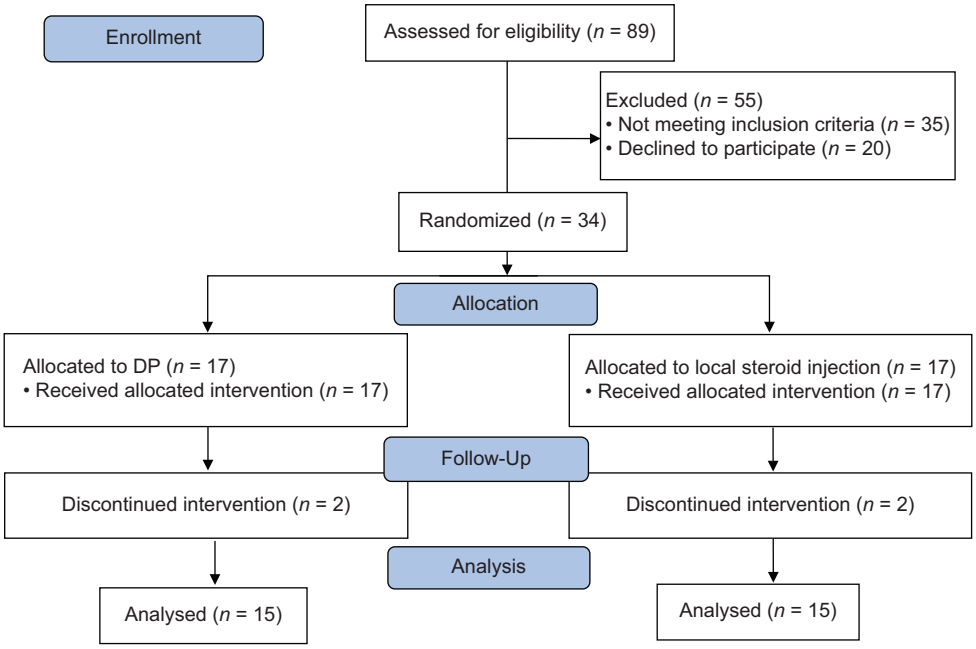

Figure 1: Participant-flow algorithm.

Table 1: Baseline characteristics of participants

Characteristics	Group A (n=17)	Group B (n=17)	P	Mean difference/odds ratio (95% CI)
Age (years)	41.35±10.75	43.4±7.6	0.52*	2.059 (8.568-4.451)
Sex (female : male)	08 : 09	09 : 08	0.73†	0.790 (0.205-3.038)¶
Durations of symptoms (weeks)	36.71±22.82	27.29±33.06	0.32*	9.412 (9.629-28.452)
Laterality of pain (right : left)	14 : 03	14 : 03	1‡	1 (0.171-5.833)**
VAS	7.00±1.73	6.35±1.41	0.16*	0.647 (0.26-1.554)
DASH	37.52±16.16	33.83±14.77	0.49*	3.694 (7.124-14.512)
PFGS	13.29±8.36	9.76±7.10	0.19*	3.529 (1.892-8.951)

CI, confidence interval; DASH, disabilities of the arm, shoulder and hand scale; PFGS, pain-free grip strength; VAS, visual analog scale. *Independent test. †χ^2-test. ‡Fisher exact test. ¶Odds ratio of male with reference to female for group B with respect to group A. **Odds ratio of right with reference to left for group B with respect to group A.

Table 2: Comparison of outcome measures between group A and B

Time points	Group A (n=15)	Group B (n=15)	P	Mean difference (95% CI)
Pain in terms of VAS score				
At baseline	70±12.5	63.3±14.9	0.19*	0.667 (0.366-1.699)
At fourth week	53.6±12.6	51.3±15.5	0.65*	0.233 (0.824-1.291)
At eightth week	42±13.2	41.6±6.7	0.93*	0.033 (0.75-0.817)
At 16th week	30.3±10.2	44.3±8.4	0.0003*	1.4 (2.102-0.698)
P	<0.0001§	<0.0001§	-	
DASH score				
At baseline	37.7±17.3	33.8±15.8	0.52*	3.86 (8.511-16.231)
At fourth week	26.2±14.6	26.7±15.6	0.93*	0.48 (11.787-10.827)
At eighth week	22.4±13.6	18.9±9.4	0.43*	3.427 (5.306-12.159)
At 16th week	21.6±10.7	13.2±4.4	0.42*	2.813 (9.98-4.354)
P	<0.0001§	0.004§	-	
Pain-free grip strength (PFGS)				
At baseline	13.1±8.9	9.5±7.5	0.24*	3.6 (2.559-9.759)
At fourth week	16.3±8.7	12.3±5.4	0.14*	4 (1.419-9.419)
At eighth week	19.1±9.8	14.4±4.0	0.1*	4.667 (0.946-10.279)
At 16th week	21.6±10.7	13.2±4.4	0.009*	8.4 (2.271-14.529)
P	<0.0001§	0.008§	-	

CI, confidence interval. *Independent test. §Paired t-test.

elbow. They demonstrated improvement in pain and isometric strength scores compared with the control group in which normal saline was injected. The effect was maintained at long-term follow-up [3]. Compared with them, in this study, we used higher concentrations of dextrose (12.5%). Our findings showed improvement in both the DP and steroid groups at the third-month follow-up. However, DP proved to have significantly better and longer effects. This finding is consistent with a recent study that has suggested inferior long-term efficacy of steroids than other treatments for chronic LE [21].

In contrast, in 2011, Crayannopoulos *et al*.[20] compared prolotherapy (phenol 1.2%, glycerin 12.5%, and dextrose 12.5% in sterile water) versus methylprednisolone 40 mg/ml in a double-blinded RCT. After a 6-month follow-up, they detected a significant improvement in the functional status (based on DASH) of both groups, but VAS scores did not show significant changes in the steroid group. Finally, their conclusion did not support any superiority of prolotherapy to steroids. However, they stated that it might be due to a lack of statistical power.

Rabago *et al*. [19], in 2014, in a three-arm RCT, evaluated 26 patients with chronic LE comparing DP, dextrose–morrhuate sodium, and conservative treatment of wait-and-watch. The results revealed a significant improvement in the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire score for both prolotherapy groups. However, the grip strength improved only in the DP group, as was seen in our study [19].

In 2014, Sims *et al*. [2], in a systematic review, assessed the efficacy of nonsurgical treatments of LE, including various types of injections, bracing, and physical agent modalities such as extracorporeal shockwave therapy and low-level LASER. Regarding the effectiveness of local steroid injection, they reported a short-term improvement in pain and function, but the results did not support the long-term benefits of the steroid [22–24]. They also evaluated and reviewed the efficacy of the prolotherapy method in three studies [3,25]. Only one of them compared the prolotherapy with steroid injection, exactly similar to our investigation [20]. However, that study was inconclusive due to the high amount of loss to follow-up (29%).

Similarly, Krogh and colleagues evaluated several RCTs and finally concluded that in contrast to steroids, prolotherapy was significantly better than placebo [3,13,26]. Last, in 2018, Dwivedi and colleagues reviewed articles working on the utility of prolotherapy in the upper-extremity. Their study proved the beneficial effects of prolotherapy for upper-extremity pathology such as hand osteoarthritis, LE, and rotator-cuff disease as it is safe and cost-effective [27]. Recently, Bayat *et al*.[28] detected a short-term efficacy for a local steroid injection, with prolotherapy revealing longer and higher therapeutic effects.

Inculcating the results of the present study and other previous studies, the fact remains clear that both therapies have therapeutic results on account of the specific mechanisms. On one hand, corticosteroids decrease the inflammatory cascade and suppress the local immune response to pain, and thus help in the treatment of LE [16], while prolotherapy injections act via the hypertonic solution (dextrose) base that causes cell rupture through osmosis, increases the expression of platelet-derived growth factor while the monosodium morrhuate attracts inflammatory mediators, and improves blood supply to the diseased tendon. Moreover, hypertonic dextrose is also a mild vascular sclerosant [20].

Overall, it can be seen that DP has a wider range of actions that corroborate with the present study results of better and longer effects in treating chronic tennis elbow.

Limitations

The major limitation of this RCT was the small sample size. However, compared with the previous studies [3,19,20], that was acceptable. On the other hand, it should be emphasized that the double-blinded RCT design, validated patient-oriented outcome measure, and minimal data loss were our strengths. In the future, larger RCTs with a longer duration of follow-up are needed.

Conclusion

This study showed a significant improvement in pain, improved upper-extremity activities, and PFGS in both the DP and steroid injection groups during 1-month follow-up. However, in the DP group, this improvement persisted even after 3 months, while in the parallel group, steroids only provided a short-term improvement. To summarize, DP had significantly longer effects in treating LE.

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Conflicts of interest

There are no conflicts of interest.

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