Healing effects of prolotherapy in treatment of knee osteoarthritis healing effects of prolotherapy in treatment of knee osteoarthritis

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Purpose
Prolotherapy is an injection therapy for chronic musculoskeletal pain. We conducted a two-arm controlled trial to assess the efficacy of prolotherapy for knee osteoarthritis (OA).

Materials and methods
A total of 104 adults with at least 6 months of painful primary knee OA were treated with dextrose prolotherapy (group I). They were divided into two subgroups: Ia and Ib. Subgroup Ia was treated with both techniques of prolotherapy (Hackett technique – classic, traditional prolotherapy – and Lyftgot technique – neural prolotherapy), whereas subgroup Ib was treated with the Hackett technique only. Extra-articular and intra-articular injections were administered at 1, 2, and 3 months, with as needed additional treatments at months 4 and 5. A total of 24 adults with at least 6 months of painful primary knee OA were treated with physiotherapy (group II). Outcome measures included the following: clinical assessment; visual analogue scale (VAS), 10; Western Ontario McMaster University Osteoarthritis Index (WOMAC), 96 points; plain radiographs; and musculoskeletal ultrasound. Postprocedure hot packs were applied, and at-home massage and exercises were taught.

Results
128 Patients enrolled in the study were matched with each other for sex, age, disease durations, and BMI. Subgroups Ia and Ib reported a significant improvement as regards the clinical assessment, VAS, WOMAC, and radiological assessment at 12 months, compared with their baseline at month 0 and compared with group II ($P \leq 0.001$). At 12 months, the mean ± SD of VAS was 0.32 ± 0.27 for subgroup Ia, 0.44 ± 0.5 for subgroup Ib, and 9.9 ± 1.65 for group II, and the mean ± SD of WOMAC was 11.32 ± 10.3 for subgroup Ia, 18.5 ± 10.25 for subgroup Ib, and 79.5 ± 22.63 for group II. Postprocedure application of hot packs, massage, and paracetamol resulted in diminution of injection-related pain. There were no adverse events.

Conclusion
Prolotherapy resulted in clinically sustained improvement of pain, function, and radiological assessment, which means that the healing effects of prolotherapy is better than that of physiotherapy. The combination of the two prolotherapy techniques results in quicker and better improvement for patients in terms of the clinical assessment, VAS, and WOMAC.

Keywords:
knee osteoarthritis, knee plain radiographs, ligaments and tendons, musculoskeletal ultrasound, prolotherapy

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Introduction

Knee osteoarthritis (OA) is a chronic disease resulting in joint pain, stiffness, and decreased function. It is a common and expensive disability for patients and society, and it is age related [1]. Conservative therapies and oral supplements have been evaluated, but are without clear efficacy; however, a recent systematic review reported no clear benefit of any one therapy. The Agency for Healthcare Research and Quality has called for the development of new therapies to prevent and treat knee OA [2]. Prolotherapy is an injection therapy designed to stimulate healing of chronic musculoskeletal injury, including knee OA [3]. It is a fundamental and an effective therapy for the repair of injured fibrous connective tissue and thus makes them tighter and stronger [4]. These tissues include ligaments, tendons, muscle fascia, joint capsules, and cartilage on the inside of the joints [5,6]. When the connective tissue is weak, there is insufficient tensile strength and the normal tension stretches the relaxed fibers, resulting in stimulation of sensory fibers and thereby causing pain [3,7,8]. A core principle is the injection of small volumes of a proliferant solution at multiple painful ligament and tendon insertions, in adjacent

joint spaces, along the superficial cutaneous nerves, and their chronic constriction injuries over several treatment sessions [3,9]. Contemporary hypotheses suggest that prolotherapy stimulates local healing of chronically injured extra-articular and intra-articular tissues, although definitive evidence is lacking [2]. It causes localized inflammation, which initiates the influx of inflammatory cells, and, on maturation of the collagenous fibers, fibrous tissue becomes shrunken and shorter [10–12]. It also stimulates articular cartilage regeneration [13-15]. Dextrose is a commonly used injectant [2]; its hypertonic solution stimulates mild degree of local inflammation [16], whereas the hypotonic solution inhibits the neurogenic inflammation by blocking transient receptor potential vanilloid type 1. Transient receptor potential vanilloid type 1 is a nonspecific membrane cation channel that allows the influx of Na^+ and Ca^{2+}, in which Na^+ influx results in action potential and nociception, whereas Ca^{2+} influx results in the release of neuropeptides, Substance P and calcitonin gene-related peptide [9], which cause tissue inflammation and edema, tissue calcification, tissue collagenolysis, stress fractures, increase in intramuscular compartment pressure, cause muscle spasm, and lead to neuropathic pain [17].

Materials and methods

The study was approved by the Ain Shams University Human Subject Ethical Committee Review Board. The 128 patients enrolled in the study were recruited from Ain Shams University Hospitals, from the rehabilitation clinics. Inclusion criterion was a diagnosis of knee OA based on clinical criteria (American College of Rheumatology) [10] with at least 6 months of pain. Exclusion criteria included cancers and under-nutrition in order not to interfere with the healing process of the body. Secondary knee OA cases were excluded as well, such as osteoarthritis associated with any autoimmunediseases, gouty arthritis, hormonal imbalance, infectionor hematological disorders. Each knee was assessedseparately for eligibility. Eligible individuals attended an informational meeting, gave consent for participation, and were enrolled in the study.

Study design

Patients in group I were subjected to dextrose prolotherapy. Subgroup Ia was treated with the Hackett technique – classic traditional prolotherapy – [3] and Lyftgot technique – neural prolotherapy [9], whereas subgroup Ib was treated with the Hackett [3] technique alone. Hackett described his technique as 'welding', because prolotherapy works as spot welding and strengthens the exact spots at fibro-osseous junctions where the injections take place [3]. Hilton's law postulated that nerves supplying the joints are the same ones that supply the muscles moving these joints and the skin overlying them. The superficial nerve pathology and healing drape themselves to affect deeper anatomic structures [9]. Patients in group II were assigned to physiotherapy. All patients enrolled in this study underwent a quadriceps strengthening program before the start of the study.

Injection intervention

Injections were performed at 1, 2, and 3 months, with optional additional sessions at 4 and 5 months as per the physician's recommendations and the participant's self-assessment for pain and disability improvement. Before the procedures, the knee was examined, tender anterior–medial–lateral knee locations were marked, anesthetic skin wheals of 1% lidocaine were placed, and extra-articular and intra-articular injections were performed according to the method described in a published protocol (Table 1). Extra-articular injections were administered on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 40 ml of solution; ultrasound guidance was not used. The 5-ml intra-articular injection was then delivered using an inferomedial approach. After the injection, participants were offered acetaminophen tablets to use as needed for up to 1 week and were advised on relative knee rest

Table 1 Prolotherapy injection protocol

Injection site	Solution	Injection technique
Intra-articular 25% dextrose	In a 5 ml syringe:5 ml of 25% dextrose	A volume of 5 ml was injected using an inferomedial or an inferolateral approach
Extra-articular15% dextrose	Forty milliliters distributed in eight 5 ml syringes, constituting 24 ml of 25% dextrose, 8 ml of 1% lidocaine, and 8 ml of 0.9% saline	Up to 15 subdermal injections of lidocaine 1% were administered, and 0.5 ml of 15% solution was injected using a peppering technique with a 25-G, 2¾ inches needle at each ligament–bone insertion site. Each puncture site allowed for placement of solution at up to three ligament–bone insertions using a skin sliding technique (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing from the initial puncture site), allowing for placement of up to 40 ml of solution

for 2–4 days with progressive resumption of routine activity over 1 month. They were discouraged from using NSAIDs and from starting new therapies for their OA during the study period.

At-home exercise intervention was demonstrated to all patients at baseline. Patients were advised to begin exercises (three sessions per week, one session daily, 10 repetitions per exercise), and then gradually increase therapy as tolerated over 20 weeks (five sessions per week, three times daily, 15 repetitions per exercise), and to continue them thereafter if desired.

Outcome measures

The short-term (months 2 and 5) and long-term (month 12) follow-ups included clinical assessment, evaluation of knee-related quality-of-life as assessed with the visual analogue scale (VAS) [18] from 0 (best) to 10 (worst), and determination of composite score of Western Ontario McMaster University Osteoarthritis Index (WOMAC) [19] from 0 (best) to 96 (worst). The long-term follow-up included radiological assessment (plain radiographs), 1–4 point Kellgren–Lawrence knee OA scoring system [14], and musculoskeletal ultrasound for measuring the dimensions of the medial and lateral collateral ligaments and the patellar tendons and the thickness of the articular cartilage in both articular compartments.

Statistical analysis

The collected data were revised, coded, tabulated, and introduced to a PC using Program SPSS 7.5 (SPSS ,Inc, Chiago IL USA) for Windows (Statistical Package for the Social Science). Data were presented and suitable analysis was carried out based on the type of data obtained for each parameter.

(1) Descriptive statistics:
   (a) Mean, ± SD, and range for numerical data.
   (b) Frequency and percentage for non-numerical data.
(2) Analytical statistics:
   (a) Student's *t*-test: This test is used to assess the statistical significance of the difference between two study group means.
   (b) Wilcoxon rank sum test (*Z*): This test is used for nonparametric data to compare two paired groups. The test essentially calculates the difference between each set of pairs and analyzes these differences

Probability of error (*P* value) has a significant level at 0.05:

P value greater than 0.05 is considered nonsignificant (NS);
P value of 0.05 or less is considered significant (S); and
P value of 0.01 or less is considered highly significant (HS).

Results

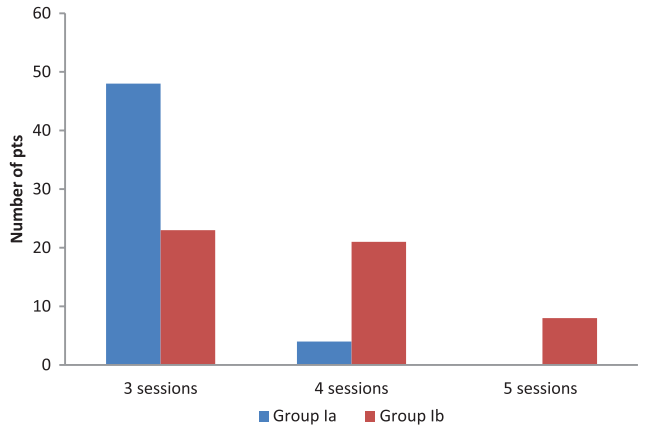
Subgroup Ia included 39 female (75%) and 13 male patients (25%). Their ages ranged from 35 to 76 years, with a mean of 51.07 ± 12.11 years. Their disease durations ranged from 1.5 months to 30 years, with a mean ± SD of 6.89 ± 9.03 years. As regards their BMI, 5.7% of patients (three patients) were of average weight (BMI=25–30), 44.3% (23 patients) were overweight (BMI=31–35), and 50% of them (26 patients) were morbidly obese (BMI > 35). Subgroup Ib included 39 female (75%) and 13 male patients (25%). Their ages ranged from 38 to 73 years, with a mean of 50.98 ± 10.5 years. Their disease durations ranged from 1.5 months to 30 years, with a mean of 6.63 ± 8.99 years. As regards their BMI, 5% of patients (three patients) were of average weight, 43% (22 patients) were overweight, and 52% of them (27 patients) were morbidly obese. Group II included 18 female (75%) and six male patients (25%). Their ages ranged from 39 to 75 years, with a mean of 52.75 ± 11.06 years. Their disease durations ranged from 1.5 months to 30 years, with a mean of 6.03 ± 8.71 years. As regards their BMI, 4% of patients (one patient) were of average weight, 46% (11 patients) were overweight, and 50% of them (12 patients) were morbidly obese.

There was no statistically significant difference between subgroup Ia, subgroup Ib, and group II as regards sex, age, disease duration, and BMI ($P > 0.05$).

There was no statistically significant difference between the three groups of patients at baseline as regards the VAS and WOMAC scores. However, at short-term and long-term follow ups, there was a statistically highly significant decrease in VAS and WOMAC for patients in subgroups Ia and Ib compared with their baseline scores ($P \leq 0.001$). Moreover, on comparing subgroup Ia with subgroup Ib as regards the VAS and WOMAC, we found that, at short-term follow-up, subgroup Ia reported a statistically highly significant improvement compared with subgroup Ib ($P \leq 0.001$). For the patients in group II, there was no statistically significant decrease in their VAS and WOMAC at short-term follow-up ($P \leq 0.05$), and there was a statistically significant (S) increase in their VAS and WOMAC at long-term follow-up compared with their baseline scores ($P \leq 0.05$).

As regards the dimensions of the medial and lateral collateral ligaments and the patellar tendons and the thickness of the cartilage in both articular compartments, there was no statistically significant difference between the three groups of patients at baseline. At long-term follow-up, we found in subgroups Ia and Ib a highly statistically significant decrease in the dimensions of ligaments and tendons ($P \leq 0.001$) and a highly statistically significant increase in the articular cartilage thickness in both compartments ($P \leq 0.001$). For group II, there was a highly statistically significant increase in the dimensions of ligaments and tendon ($P \leq 0.001$) and a highly statistically significant decrease in the articular cartilage thickness in both compartments ($P \leq 0.001$). There was a statistically high significant difference ($P = 0.001$) between the patients in group "Ia" and the patients in group "Ib", regarding the different number of injection sessions needed by each sub-group, during the treatment period of the study (Fig. 1) where group "Ia" needed less number of injection sessions than group "Ib".

Figure 1

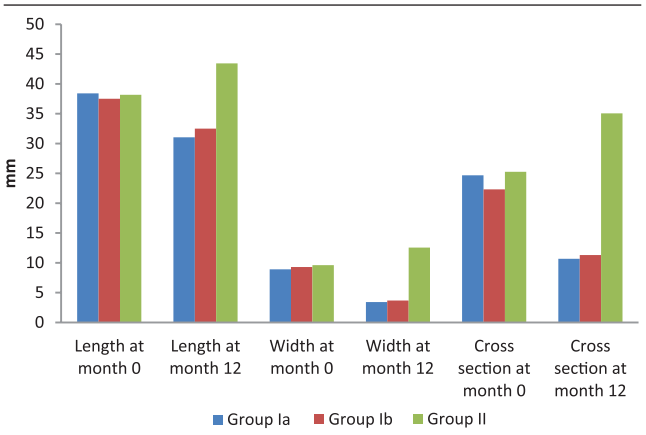


Different number of injection sessions needed by subgroup Ia and subgroup Ib; subgroup Ia needed fewer injection sessions compared with subgroup Ib during the treatment period of the study.

Figure 2 presents the dimensions of the medial collateral ligaments for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months. Fig. 3 presents the dimensions of the lateral collateral ligaments for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months. Fig. 4 presents the dimensions of the patellar tendons for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months. Fig. 5 presents articular cartilage thickness in the medial and the lateral articular compartments for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months.

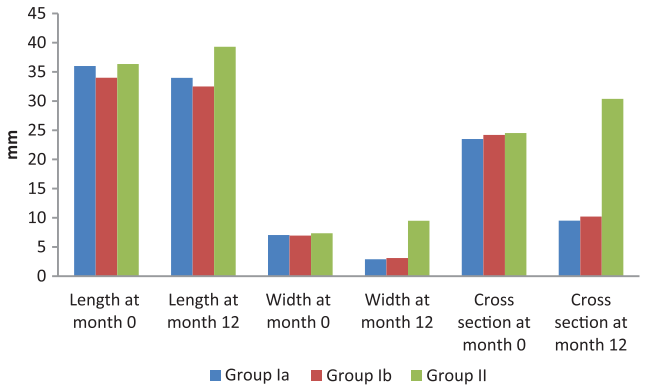
At baseline, there was no statistically significant difference between the three groups of patients as regards their radiological findings. At long-term follow-up, there was a highly statistically significant improvement for the patients in subgroups Ia and Ib ($P \leq 0.001$), and there was a highly statistically significant decrement for the patients in group II as regards the radiological grades of their knee OA ($P \leq 0.001$). There was a statistically high significant difference ($P = 0.001$) between the

Figure 2



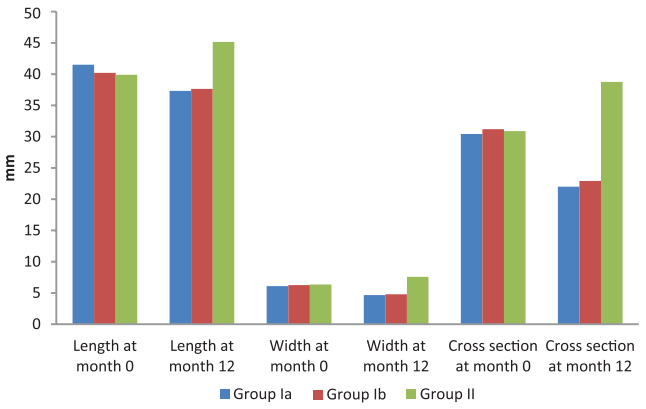
Dimensions of the medial collateral ligaments for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months.

Figure 3



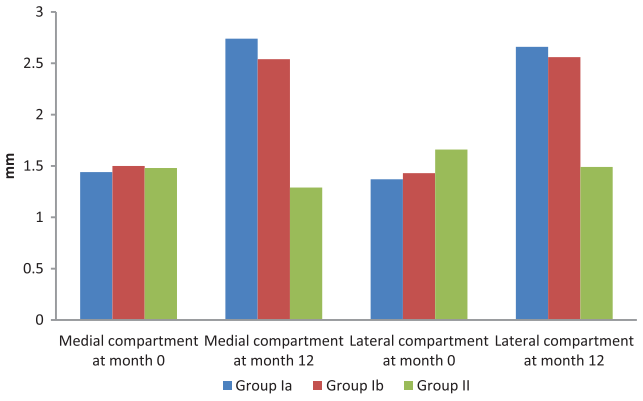
Dimensions of the lateral collateral ligaments for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months.

Figure 4



Dimensions of the patellar tendons for the patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months.

Figure 5



Articular cartilage thickness, in the medial and lateral articular compartments, for patients in subgroup Ia, subgroup Ib, and group II at 0 and 12 months.

patients in group "Ia" and the patients in group "Ib", regarding the different number of injection sessions needed by each sub-group, during the treatment period of the study (Fig. 1) where group "Ia" needed less number of injection sessions than group "Ib".

Discussion

Prolotherapy stimulates healing and improves repair and reconstruction of ligaments and tendons in patients with chronic knee OA and it stimulates articular cartilage regeneration as well. Consequently, it decreases the chronic pain of the knee, increases the knee stability, and improves the knee function.

Our study revealed that patients treated with dextrose prolotherapy (group I) showed a better clinical and radiological improvement compared with patients treated with physiotherapy (group II). This was reported in the studies conducted by Reeves and Hassanein [8] and Hauser [6] as well. This is attributed to the regenerative effect of prolotherapy on the ligaments, tendons, and cartilage, which improves the signs and symptoms during the clinical assessment and the radiological findings [6, 8].

Our study revealed that patients treated with dextrose prolotherapy (subgroups Ia and Ib) showed a highly statistically significant decrease in their VAS and WOMAC compared with those at baseline. This is in accordance with the study of Rabago *et al.* [1] and Rabago *et al.* [2]. This is explained by the regenerative and reconstructive effect of prolotherapy, which resulted in an increase in knee function [1,9,12]. Moreover, our study revealed that there was a highly statistically significant difference in the decrease of VAS and WOMAC throughout the year between the patients in subgroup Ia and subgroup Ib. This is attributed to the effect of the combined prolotherapy techniques used in the treatment of subgroup Ia, whereas subgroup Ib received only one technique of prolotherapy in their treatment.

By re-assessing our patients at long-term follow-up, we found a highly statistically significant improvement in their plain radiographic grades compared with baseline data. A similar finding was documented by Hauser [6], Reeves and Hassanein [16], and Solmaz *et al.* [15]. This is attributed to the fact that prolotherapy stops the neurogenic inflammation [9] and thus stimulates articular cartilage regeneration [13].

Moreover, by using the musculoskeletal ultrasound in our study, we were overwhelmed by the finding that the ligament dimensions revealed a highly statistically significant decrease at the long-term follow-up as regards the medial and lateral collateral ligaments and the patellar tendons for the patients in group I compared with their baseline values (month 0). Although this finding was previously confirmed by Aneja *et al.* [20] and Rabago *et al.* [12] on rats, the results were promising enough to be tested on humans. This could be attributed to the localized inflammation caused by prolotherapy, which initiates the influx of inflammatory cells, and, on maturation of the collagenous fibers, fibrous tissue becomes shrunken and shorter [11].

The long-term radiological follow-up (month 12) of the patients in our study, using the musculoskeletal ultrasound, revealed a highly statistically significant increase in the articular cartilage thickness in both medial and lateral articular compartments for the patients in group I compared with their baseline (month 0). This is in agreement with the studies of Reeves and Hassanein [8] and Hauser [6]. An explanation of that could be that prolotherapy, by stopping the neurogenic inflammation and inhibiting the release of the neuropeptides substance P and calcitonin gene-related peptide, results in articular cartilage regeneration [9].

In conclusion, combining both techniques of prolotherapy gives better and quicker response in healing and tissue regeneration, as well as in VAS and WOMAC.

Conclusion

Prolotherapy treatment is a line of conservative therapy that gives better positive and promising results for the patients compared with physiotherapy. Prolotherapy

improved knee OA as it stimulated the regeneration of ligaments, tendons, and articular cartilage; consequently, it decreased knee pain and increased knee stability and function. Plain radiographs showed that prolotherapy improved the grades of knee OA. Musculoskeletal ultrasound showed that prolotherapy decreased the ligament and tendon dimensions and increased the articular cartilage thickness. Combining neural with classic traditional prolotherapy gave quicker and better improvement compared with classic prolotherapy alone.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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