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Original Article

Long-term Efficacy of Dextrose Prolotherapy versus Hyaluronic Acid in Knee Osteoarthritis

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Keywords
Osteoarthritis of knee; Hyaluronic acid; Dextrose; Prolotherapy; Intra-articular injection

Abstract

Background: Osteoarthritis (OA) is the most common form of arthritis. Management of OA includes lifestyle modification, exercise, supportive care, weight control, pharmacological treatment, intra-articular injection, and surgery. Due to little knowledge about knee prolotherapy, in this study, we investigated the efficacy of prolotherapy for knee OA compared with hyaluronic acid (HA).

Methods: In this prospective randomized blinded clinical trial, after the diagnosis of OA, the range of motion (ROM), joint line tenderness, pain intensity [visual analog scale (VAS) score], and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire were evaluated. Randomization was performed by concealed allocation using computer software. The participants, outcome assessor, physical examiner, and radiologist were blinded to injection group status. Three intra-articular injections (every month in prolotherapy group and every week in the HA group) were performed. Patients at one week, one month, three months, eight months, and nine months after the end of treatment were re-evaluated.

Results: A total of 130 patients were screened and finally 61 patients in the HA group and 53 in the dextrose prolotherapy group completed the study. In the dextrose prolotherapy group, changes in joint ROM had an upward trend, but pain intensity and the total WOMAC score constituted a downward pattern and in the HA group, maximum improvement was achieved between 4 to 6 months after the last injection, followed by a slightly progressive worsening after 6 to 12 months. The final clinical scores remained higher compared with baseline in both groups ($P < 0.001$). The mean scores for all patients significantly improved ($P < 0.001$ for VAS and $P < 0.030$ for ROM) from baseline to months 6 and 12. However, dextrose prolotherapy group had a significantly greater improvement ($P < 0.001$) than HA group.

Conclusion: Dextrose prolotherapy showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function. Therefore, it can be a good choice for the treatment of knee OA.

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Introduction

Osteoarthritis (OA) is the most common form of Arthritis.[1] The prevalence of OA varies significantly depending on the definition used, age, sex, and geographical area. The estimated total prevalence of radiographic OA in the United States of America (USA), Europe, and Japan ranges from 36% to 48% of the population.[2] The most frequently affected joints by OA are the knee (33.0%), hand (29.5%), foot (20.8%), and the hip (4.7%). Incidence rate increases with age and women have a higher rate than men, especially after age 50.[3]

Pain is the dominant symptom in OA which is typically related to joint overuse and is relieved by rest. Progression of the OA process causes persistent pain which leads to pain at rest and at night. According to American College of Rheumatology (ACR), diagnosis of OA is based on history, physical examination, and X-ray images [Kellgren-Lawrence (KL) method].[4]

Management of OA includes lifestyle modification, exercise, supportive care, weight control, pharmacological treatment, intra-articular injection, and surgery.[5,6] Different intra-articular injection substances include corticosteroids, hyaluronic acid (HA), and dextrose. Unfortunately, corticosteroids can cause adverse side effects (such as joint degradation) when injected indiscriminately over long periods of time directly into the joint. Therefore, they should be used only to treat an occasional flare of OA, particularly in younger people.[7]

Injectable HA is a treatment approved by the Food and Drug Administration (FDA) for knee OA. This form of therapy, known as "viscosupplementation", involves the injection of HA in the joint once a week for three to five weeks in a row. HA injection may provide pain relief up to 12 months, but there is no evidence that the treatment alters the progression of the OA process and also, to date, there is little information on the long-term effects of HA injection.[8] Dextrose injections have been hypothesized to stimulate healing of chronically-injured extra-articular and intra-articular tissue.[9] Animal model studies have reported increased inflammatory markers[10] and a significantly enlarged cross-sectional area in medial collateral ligament (MCL).[11] The potential of prolotherapy to stimulate release of growth factors favoring soft-tissue healing[12,13] and a positive neural effect have also been suggested.[14] because of the little knowledge about knee prolotherapy, in this study, we investigated the efficacy of prolotherapy for knee OA compared with HA.

Methods

This study is a prospective randomized blinded clinical trial that was approved by the Research Ethics Committee of Imam Reza Hospital, Tehran, Iran. During 2012 to 2013, all patients with knee OA diagnosed by clinical criteria of the ACR (pain, over than 50 years old, less than 30 minutes of morning stiffness, crepitus on motion, bony enlargement, no palpable synovial warmth) with a radiographic score of II on the KL scale [minute osteophyte and doubtful significance (grade 1), definite osteophyte and unimpaired joint space (grade 2), moderate diminution of joint space (grade 3), and joint space greatly impaired by sclerosis of subchondral bone (grade 4)] who had at least 3 months of knee pain and normal general physical examination were included. Patients with significant medical comorbidities [including diabetes, cardiovascular disease (CVD)], anticoagulation therapy, body mass index (BMI) greater than 40 kg/m^2, rheumatoid arthritis (RA) or other forms of inflammatory arthritis, gout, past history of total knee arthroplasty (TKA) or arthroscopy, previous intra-articular injections, and alcohol or opium abuse were excluded.

Patients signed a written informed consent before participation and were also asked to

discontinue all current medications and non-pharmacological therapies for knee OA 48 hours before the study, but they were allowed to use acetaminophen if necessary. Patients were randomly assigned to one of two injection groups: dextrose or HA. In patients with bilateral knee OA, the more painful knee was assessed but intra-articular injection was performed for both knees.

Randomization was performed by concealed allocation using computer software. The participants, outcome assessor, physical examiner, and radiologist were blinded to injection group status. But, because of the obvious differences in the volume administration of sodium HA solution versus dextrose, intra-articular injection was performed by an unblinded physician other than the blinded investigator. Since the treatment was not blinded and the time intervals between HA and dextrose injections were different, the treatment was randomly allocated to each group of patients.

The HA group received one weekly injection of 2 ml sodium hyaluronate solution 1% (Hyaluron HEXAL, manufactured by Lifecore Biomedical, LLC) over two weeks for a total of 3 injections (day 0, day 7, and day 14). The dextrose group received an injection of 9 ml dextrose 20% + 1 ml lidocaine 2% every month, over two months for a total of 3 injections (day 0, month 1, and month 2). All injections were administered under sterile conditions using an inferomedial approach.

Demographic data, including age, sex, weight, height, BMI, and duration of disease were recorded. The findings on the initial radiographs were graded by a radiologist. Range of motion (ROM) (goniometrically-measured knee flexion range) was assessed by a specialist.

The primary recorded data (demographic and radiologic grading) were preserved by the investigators and no one else had access to them. Since symptom duration is a potential confounding factor and will be a baseline variable predicating outcome, it was important to be the same in the two groups. On the other hand, this factor may also have a direct relationship with the patient's age. Therefore, stratified randomization was also used based on age, sex ratio, and symptom duration. The patients were evaluated for their baseline characteristics, radiographic findings, compliance with the treatment, clinical manifestations, safety, and adverse events (infection, hemarthrosis). Pain levels in up and down stairs test were evaluated by visual analog scale (VAS, 0 to 100 mm). The clinical manifestations were evaluated by the composite score of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a validated questionnaire evaluating OA severity using pain, stiffness, and function subscales. The WOMAC composite score, constructed as the weighted average of the three subscale scores, ranges from 0 (the worst) to 100 (the best) knee-related quality of life and has been shown to be responsive to change. But the scoring system of the WOMAC questionnaire is not specific to one knee and involves activities that are influenced by symptoms in both knees. On the other hand, it should also be noted that, for the grading of knee OA, the KL method and X-ray imaging were obtained from each knee with different scores. Finally, each patient would have two X-rays, with the same scoring or different (for example, left knee with grade 2 and right knee with grade 3). Because of these points, patients can be divided to several categories: only one of the two knees with grade 2 and another one with grade 1 or zero (mild) (in this category injection is performed only for the knee with grade 2), both knees with grade 2 (moderate), one or both of knees with grade 3 (severe), and at least one knee with grade 4 (very severe). In this study, there were only 5 patients who were placed in the mild category and injection was performed only for one knee.

The patients were re-evaluated monthly up to 12 months after the last injection, but for facility of comparison, the changes in each of the outcome variables from step 1 (at the

onset of study, before intervention) to steps 2 and 3 (6 and 12 months after the last injection) were compared between groups.

Data management and statistical analysis were performed by using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Frequencies and percentages were used to describe the categorical variables and the mean, standard deviation (SD), and standard error of the mean (SEM) were used for quantitative variables. Statistical evaluation of the difference in proportions was performed using chi-square test and Fisher's exact test. Mean differences between the two groups were evaluated using independent t-test. Changes in pain severity (VAS scores) and joint ROM were evaluated using the repeated measures analysis of variance (ANOVA). Within-group analyses were conducted to assess change in the outcome variable using paired Student t-test. In non-parametric data, the Wilcoxon's signed-rank test was used. Between-group analyses were conducted using the independent samples t-test. Significance of the tests was expressed by a P-value less than 0.05.

Results

A total of 130 patients were screened, 65 patients in each group. In the HA group, 3 patients used non-steroidal anti-inflammatory drugs (NSAIDs) (one due to low back pain and 2 because of trauma or accident) and one patient had a cardiovascular event. In the dextrose group, 3 patients consumed NSAIDs (2 patients due to low back pain and one because of trauma or accident), 3 patients had cardiovascular events, 2 patients had cerebrovascular events, and 4 patients lost the follow-up due to immigration (Figure 1).

There were not important or significant adverse events or complications (such as infection, hemarthrosis, etc.) during the study, unless worsening in pain intensity 1 to 3 days after any injection which was predictable.

After excluding some patients from the analysis, data were available for 61 patients in the HA group and 53 in the dextrose group. No significant differences between the two groups were found in respect to baseline demographics (age, BMI, and gender proportion) and disease characteristics (symptom duration and radiologic grading) (Table 1).

Also, no significant differences were noted between groups for pain levels in up and down stairs test (VAS scores) and WOMAC scores at baseline (Table 1). Repeated measures ANOVA indicated the overall improvement in the pain level scores and joint ROM during the study compared to baseline in both groups (Figure 2) (within-group analysis with $P < 0.001$).

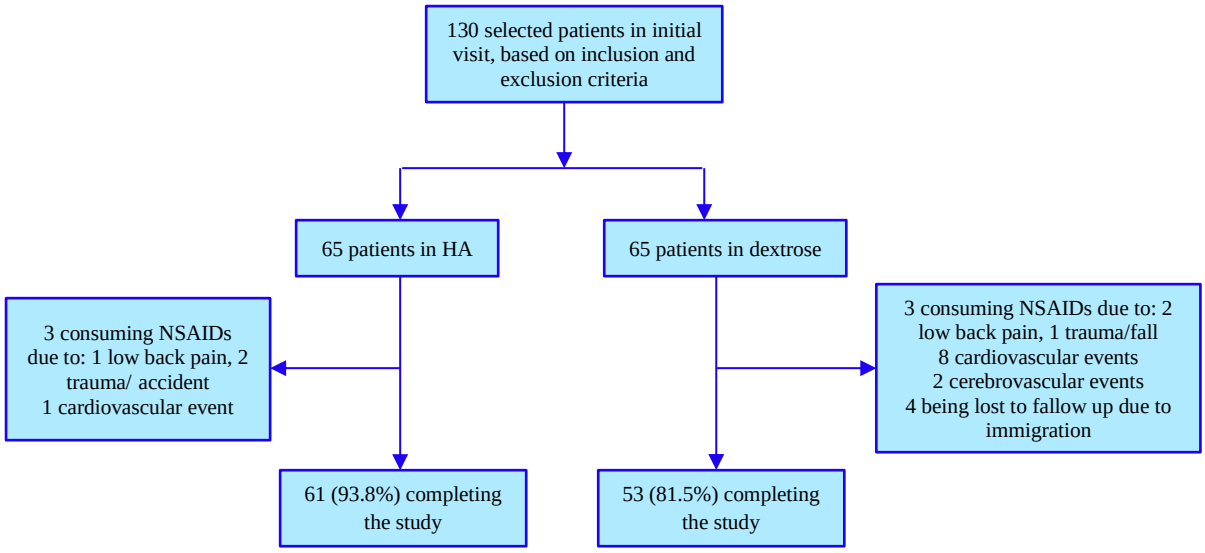

Figure 1. Flow diagram of patient enrollment and randomization
NSAIDs: Non-steroidal anti-inflammatory drugs; HA: Hyaluronic acid

Table 1. Comparison of demographic and baseline characteristics between hyaluronic acid (HA) and dextrose groups

Parameter		HA	Dextrose prolotherapy	P
Age (year)		63.88 ± 8.77	63.09 ± 9.11	0.640
Gender (female)		49 (80.32)	41 (77.35)	0.690
BMI (kg/m^2)		29.19 ± 3.26	28.73 ± 4.11	0.510
Age group > 65 years		25 (41.00)	25 (47.20)	0.500
Trauma history		10 (16.40)	10 (18.90)	0.720
Symptom duration (year)		7.82 ± 6.01	8.50 ± 6.31	0.230
Pain level in up and down stairs test		6.34 ± 1.35	6.25 ± 1.80	0.700
Knee side injection	Left	2 (3.30)	8 (15.10)	0.640
	Right	3 (4.90)	1 (1.90)	
	Bilateral	56 (91.80)	44 (83.00)	
OA severity	Mild	1 (1.60)	3 (5.70)	0.210
	Moderate	35 (57.40)	38 (71.70)	
	Severe	25 (41.00)	12 (22.60)	
Kellgren-Lawrence scale for each knee	Grade 2	79 (67.52)	79 (81.44)	0.020
	Grade 3	38 (32.48)	18 (18.55)	
Total		61	53	

Data are presented as mean ± standard deviation (SD) or frequency and percentage
HA: Hyaluronic acid; BMI: Body mass index; OA: Osteoarthritis

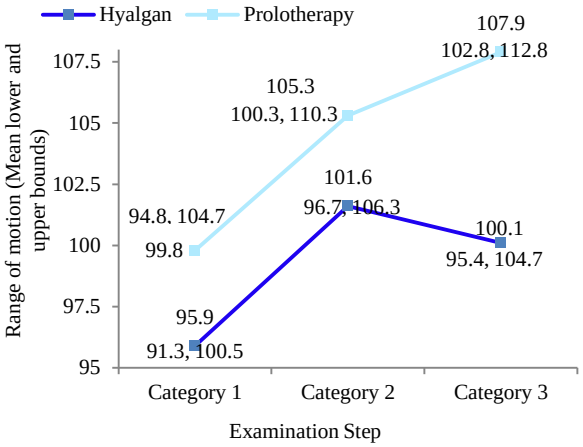

Figure 2. Comparison in range of motion (ROM) between dextrose and hyaluronic acid (HA) groups

In the dextrose group, the changes in joint ROM had an upward trend, which maintained this pattern throughout the study. On the contrary, the changes in pain intensity and the total WOMAC score constituted a downward pattern and mean values reached the bottom with a constant slope.

In the HA group, the pattern was different; maximum improvement was achieved between 4 to 6 months after the last injection, followed by a slightly progressive worsening during 6 to 12 months. The final clinical scores remained higher compared with baseline in both groups ($P < 0.001$). The mean scores for all patients significantly improved ($P < 0.001$ for VAS and $P < 0.030$ for ROM) from baseline to months 6 and 12. However, the dextrose group had a significantly greater improvement ($P < 0.001$) than HA group (Table 2).

Table 2. Comparison of post-treatment measurements in different follow-ups between hyaluronic acid (HA) and dextrose groups

Parameter	Intervention	n	Mean ± SD	P
ROM (1-6 months after injection)	HA	61	5.73 ± 6.24	0.840
	Prolotherapy	53	5.50 ± 5.94	
ROM (1-12 months after injection)	HA	61	4.18 ± 6.71	0.030
	Prolotherapy	53	8.05 ± 6.69	
Pain level in up and down stairs test (1-6 months after injection)	HA	61	2.24 ± 1.44	0.880
	Prolotherapy	53	2.20 ± 1.47	
Pain level in up and down stairs test (1-12 months after injection)	HA	61	1.45 ± 1.11	< 0.001
	Prolotherapy	53	2.45 ± 1.35	
Total WOMAC difference between month 1 and month 6 after injection	HA	61	32.20 ± 21.70	0.150
	Prolotherapy	53	41.10 ± 28.53	
Total WOMAC difference between month 1 and month 12 after injection	HA	61	27.39 ± 12.41	0.012
	Prolotherapy	53	51.00 ± 26.23	

ROM: Range of motion; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SD: Standard deviation
Our findings showed gender-related differences in treatment response for the dextrose group that was more effective in women ($P < 0.05$). Effectiveness of the medications was not associated with age and BMI in either groups.

Discussion

The present study evaluated the efficacy of intra-articular injection of dextrose compared with HA in the treatment of knee OA. HA is a natural constituent of joint fluid. Intra-articular injections of HA for the treatment of knee OA have been shown to reduce the pain and improve joint function. Recent data support the application of dextrose prolotherapy as an effective and safe method in the treatment of knee OA.[15,16] Our study did not include a placebo group. Both intra-articular therapies have been found to be superior to placebo injections.[12,13] Injectable HA is a new FDA-approved treatment for knee OA. Also, in this study, intra-articular injectable HA was considered as the standard treatment. This study clearly demonstrated that both intra-articular injections of HA and dextrose 20% significantly improved clinical symptoms (pain, stiffness, etc.) and knee joint function (ability to walking, joint ROM, etc.), but dextrose prolotherapy showed more and longer efficacy than HA injection in reducing pain and symptoms and recovering articular function. In human trials, Reeves and Hassanein showed significantly improved ligamentous stability and knee flexion in patients with anterior cruciate ligament (ACL) laxity 36 months after hyperosmolar dextrose injections.[14] In this study, the improvement in ROM in the 6th month of treatment was 13.24 degrees in the active group and 7.69 in control group; however, our study did not show any significant improvement in flexion in the 6th month, but in the 12th month, this difference was lower (8.05 vs. 4.18). Reeves and Hassanein have reported significant reduction in pain, as well as radiologic improvement in patients with knee OA,[10] but in our study, the mentioned improvement was not found in either groups.

In contrary to Reeves and Hassanein, we did not find any difference in ROM, pain, and WOMAC score in the 6th month of treatment,[10] but similar to our study, improvements in pain and WOMAC score were shown in the 54th week of treatment in the Rabago et al. study[17] and in 36th week of treatment in the Dumais et al. study[18] although Dumais et al. showed that after 36 months, there was not any difference in improvement of pain in injection of dextrose inside the knee joint and in the collateral ligaments. We can conclude that the long-term effect of dextrose prolotherapy is significant, which is seen in other studies.[19]

As we showed that women benefited dextrose prolotherapy more than men, this gender-related difference in treatment response for the dextrose prolotherapy group was also seen in previous studies.[13,14] In addition, HA is an expensive drug but dextrose has a lower price and is easily available particularly in developing countries. It seems that dextrose prolotherapy is an available and cost-effective modality in knee OA.

In this trial, we had some limitations such as obvious differences in the time interval and volume of administration of the two drugs. Another limitation of this study was the lack of a third control group treated by placebo.

Conclusion

Dextrose prolotherapy showed more and longer efficacy than HA injection in reducing pain and symptoms and recovering articular function. Long-term beneficial effects of 20% dextrose prolotherapy in comparison with short-term and medium-term effects of HA were significant. As dextrose has lower price and is easily available particularly in developing countries, it can be a good choice for the treatment of knee OA.

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Conflict of Interest

Authors have no conflict of interest.

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