Original Article

Early Effects of Hypertonic Dextrose versus Corticosteroid on Pain and Activity, in Knee Osteoarthritis; A Randomized Clinical Trial

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Abstract

Background: Knee osteoarthritis is highly prevalent and causes debilitating pain, progressive movement limitation, and significant socio-economic costs. Intra-articular corticosteroids are widely used to control it, but only short-term effects have been proven for them. Also, they have shown many local and systemic side effects, including cartilage destruction and infection susceptibility. Knee prolotherapy in various forms of hypertonic dextrose injection has shown significant restorative effects, long-lasting pain and activity improvement, negligible side effects, and low cost. The objective is to compare the early effectiveness of intra-articular dextrose with corticosteroids regarding pain and activity changes in knee osteoarthritis.

Materials and Methods: In this short-term blinded randomized clinical trial, 70 participants (knees) with primary osteoarthritis grade II or more were divided (1=1) into two random groups that received a single injection of triamcinolone 40 mg or hypertonic dextrose 20% five cc. Visual analog score (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score for activity were assessed before, one week after, and one month after injection. The data was analyzed using independent t-test, chi-square, Fisher's exact tests, Repeated measure test, and the linear mixed model regression.

Results: The rest and activity VAS score and WOMAC score were reduced in both groups one week and one month after injection, and the difference between the two groups was non-significant for the VAS score but significant for the WOMAC score in favor of the dextrose group.

Conclusion: The early analgesic and activity-improvement effects after hypertonic dextrose injection in the arthritic knee are significant and comparable to corticosteroids.

Keywords: Knee osteoarthritis, Intra-articular corticosteroid, Prolotherapy, Hypertonic dextrose

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Introduction

The knee joint (KJ) disease in adults is the most common joint disease in the body[1]. Osteoarthritis of the knee (KO) is a widespread chronic destructive (degenerative) disease in which the joint space is reduced, cartilage destruction and underlying bone changes occur, and osteophytes or bony spurs are

formed around the joint. These changes cause mild to severe pain and movement restriction[2,3]. KO is seen more with increasing age and weight and not only causes debilitating pain and progressive movement limitation in old age and obesity but imposes a socio-economic burden on society[4].

Several various treatment modalities are performed to control osteoarthritis. Joint replacement surgery is used for advanced cases with considerable cost, risks, and limitations, and for moderate and mild cases, a variety of conservative treatments are used with different degrees of cost, effectiveness, and side effects, including exercise, lifestyle changes; use of non-steroidal anti-inflammatory drugs, cartilage-building drugs like chondroitin sulfate and glucosamine; intra-articular injections of corticosteroids, hyaluronic acid and blood products such as PRP and stem cell, and also prolotherapy[5-8].

The widespread use of corticosteroids (CS) in controlling joint inflammation, including KO, dates back to the 1950s. However, extensive studies have proven only the short-term effects of CS in reducing pain and improving knee function in the first few weeks after injection. In addition, they have shown many local and systemic side effects of intra-knee corticosteroids (IKCS), including the death of cartilage cells in the KJ, accelerating the progression of osteoarthritis, subchondral fracture, osteochondrosis, and premature bone destruction, as well as suppressing the immune system and making the body susceptible to various infections. The last, in turn, obligates limiting CS usage to control acute inflammatory joint pain after the COVID-19 pandemic[9-11].

Prolotherapy is an injection therapy that uses a small volume of irritant solution to produce regenerative changes in the painful and degenerated site of the tendon, ligament, and joint space, including the knee[12]. Hypertonic dextrose (HTD) or dexter (right-handed) form of glucose is the most common injectable solution for prolotherapy, which is Inexpensive, available, safe, and with minor side effects, including injection pain and site sensitivity for up to 24 hours. The few absolute contraindications for DPT include local abscess, cellulitis, or septic arthritis. However, knowledge of a patient's anticoagulation status is important because injection at the facet level is contraindicated in the anticoagulated patient[13]. In various human clinical trials, the long-term effectiveness of HTD was proven with limited evidence of level B studies in reducing pain and improving activity in Achilles tendinopathy, rotator cuff tendinopathy, sacroiliac arthritis, lateral epicondylitis, trapeziumetacarpal joint arthritis, temporomandibular joint painful arthritis, and plantar fasciitis[14-20].

Prolotherapy of KJ has been used for over 80 years in the form of multiple and repetitive intra-articular and extra-articular injections of HTD. It has shown significant positive long-term effects in reducing pain and improving the patient's activity compared to various treatment methods[21-23]. Also, a meta-analysis study and several trials with qualitative evidence of level A study concluded that intra-articular injection of HTD in long-term KO significantly reduces pain and improves activity[24-26]. However, a few studies have compared its early effects with IKCS[27].

According to the positive results of studies based on the restorative and early analgesic effects of intra-knee dextrose (IKD) and the numerous proven complications of IKCS, it seems necessary to investigate the immediate effectiveness of HTD injection in the KJ as a CS alternative, with fewer side effects and restorative effects. This study aimed to compare the early effects of HTD and CS injection in the arthritic knee in terms of reduction of pain and activity improvement.

Methods

Ethical considerations: This study was approved by the Shahid Beheshti University of Medical Sciences (SBMU) ethics committee under IR.SBMU.RETECH.REC.1402.031 and IRCT number:20190325043107. For eligible patients, informed consent was obtained after providing the necessary explanations about the treatment process, follow-up steps, and the benefits and side effects of the intervention.

Trial design, setting, randomization, and binding: This short-term two-arm clinical trial was conducted in a single-blinded parallel randomized method. The samples were selected from patients with chronic knee pain caused by KO referred to the pain clinic of Imam Hossein Hospital and Akhtar Hospital of SBMU in 2013. The design of the study was parallel, and according to the list prepared based on the block

randomization method, the participants were allocated to two random groups, A and B, 35 cases in the CS group and 35 cases in the HTD group and they remained in the same group throughout the treatment and follow-up period. Patients did not know about the type of intervention.

Participation and eligibility: Study Inclusion criteria were 1. age range of 40 to 80 years, 2. knee pain history for at least three months that did not respond to treatment and caused activity limitation, and 3. the radiographic signs of KO: Grade II or more according to radiological Kellgren-Lawrence scale grading (the occurrence of osteophyte and reduction of joint space). Study exclusion criteria were 1. lack of participation consent in the study, 2. suffering from systemic disease such as diabetes, neurological and rheumatological diseases including rheumatoid arthritis, bleeding diseases such as hemophilia, infection of the KJ or sepsis, 3. anticoagulant or anti-platelet medication usage, 4. history of knee trauma, surgery, arthroscopy or injection in the past six months, 5. neuropathic knee pain caused by lumbar pathology, 6. pregnancy.

Sample size: Based on a previous similar study, and assuming a difference of 3.68 and a standard deviation of 2 with a non-inferiority margin of 40%, the sample size was selected at least 31 cases in each group, with a one-sided error of 0.025 and a power of 80%[28].

Interventions: Eligible patients, after signing the informed consent form, the research questionnaire was filled out for them before the injection. The research questionnaire contained questions about the amount of pain at rest and activity based on the Visual analog scoring (VAS) criteria and the ability to perform activities based on the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index.

Then, intervention was accomplished in the sterile setting, under the guidance of ultrasound, with an upper lateral suprapatellar approach and local anesthesia. Triamcinolone 40 mg and HTD 20% 5 cc were injected into group A and B, respectively. Discharge was done because there was no bleeding, swelling, or severe pain, and the vital signs were stable. The necessary points were recommended after the injection, including rest for 24 hours, intermittent use of local ice for the first few hours and starting knee exercise 48 hours later, not using NSAIDs for the first 10 days, and strict lifestyle correction and weight loss planning.

The results were evaluated for possible hematoma and infection in the visit one week later and for changes in the pain and activity level by re-answering the questions of the research questionnaire in the post-injection phase (in the visit 1week and one month later). Finally, the raw data were assessed based on statistical methods.

Outcome measures: The primary outcomes are comparing IKHTD and IKCS effects on pain during rest and activity based on the VAS score. The secondary outcomes are comparing the intervention effects on the activity level based on the WOMAC score. The comparison of the intervention effect on the level of satisfaction and the incidence of side effects at the injection site is considered.

Visual analog score (VAS): It is a 10 cm long linear pain scale numbered from 0 to 10, where the patient indicates one number depending on the felt pain severity. The zero shows no pain, 1 to 3 mild pain, 4 to 6 moderate pain, and 7 to 10 severe pain. The internal reliability of this tool has been reported as 0.85 to 0.95.

WOMAC index: The WOMAC questionnaire includes five questions about pain, two on joint stiffness, and 17 on activity limitations. Each question is scored on a scale of 0 to 4, and the total score ranges from 0 to 96, in which lower scores indicate better knee status.

Statistical analysis: Before analyzing the data, the normality of the distribution of quantitative variables was checked in both groups. The comparison was done for the mean of continuous variables using an independent t-test and for the mean of categorical variables with chi-square and Fisher's exact tests in two groups. Repeated measure test was used to evaluate the mean within-group changes of the outcomes (with adjusted BMI). Also, comparing the mean between-groups changes of the outcomes was performed with the linear mixed model regression considering the covariates of baseline BMI. All analyses were performed with SPSS.V.26 statistical software at a significance level 0.05.

Results

General variables and clinical information: The demographic characteristics in the two groups were compared in terms of age, weight, BMI, and gender, and the analysis with the relevant tests showed that there is no significant difference in terms of age and gender between the two groups (P-value= 0.484, P-value=0.780 respectively), but the mean difference of weight and BMI between the two groups was significant. Therefore, adjusted BMI in the forms of covariates of baseline BMI was used to examine the mean within-group and between-group changes of the outcomes. Also, the clinical information of the duration of chronic knee pain before the injection and the X-RAY grading of KO did not have a significant difference between the two groups (P-value=0.494 and >0.99, respectively) (Table 1).

Specific variables: The effects of IKCS and IKHTD on the pain level at rest and during activity were reducer one week and one month after injection compared to the baseline, and there was no significant difference between the two groups (P-value=0.235 and 0.285, respectively) (Table 2) (Figure 1 A and B).

The effect of both IKCS and IKHTD on the activity based on the WOMAC index was improved one week and one month after injection, and this effect was more for the HTD group than the CS group so that the two groups had a significant difference (P-value<0.001) (Figure 1-C).

Also, the within-group changes in the mean rest VAS score and activity VAS score in the HTD group significantly decreased during one month (P-value<0.001 and <0.00, respectively). However, the within-group changes in the mean rest VAS score and activity VAS score did not decrease significantly in the CS group (P-value=0.058 and 0.361, respectively).

According Table 3, the effect of HTD compared with CS was reducer for the rest and activit VAS score and for WOMAC score (β=-0.19, -0.21, and -8.38, respectively), but the average dextrose became meaningful only for WOMAC (p<0.001). The effect of time during the study showed that all outcomes decreased compared to the baseline, and these changes were significant only for VAS's outcomes. The baseline value of the outcomes significantly affected the values of changes during the study (p<0.001). It means that patients who had high values at the beginning of the study also had higher values at the end.

According to Table 4, more than 90% of Items in both groups had a satisfaction level of more than 50% one month after injection compared to the baseline (33 and 34 Items, respectively). The difference between the two groups is not significant (P-value=0.488). All members of the dextrose group agreed to continue the treatment by repeating the HTD injection 1 and 2 months after the first injection. In both groups, the patients reported no adverse effects on the next visit.

Table 1: Demographic and clinical information of the hypertonic dextrose versus corticosteroid groups for comparing early effects on pain and activity in knee osteoarthritis.

variable	HTD (n=35)	CS (n=35)	Total (n=70)	P-value
Age	67.71±8.42	66.23±9.22	66.97±8.80	0.484
Weight	79.09±8.79	74.11±7.53	76.60±8.50	0.013
BMI	29.76±2.52	27.89±2.26	28.83±2.55	0.002
		Sex		
Male	8 (47.1)	9 (52.9)	17 (100.0)	0.780
Female	27 (50.9)	26 (49.1)	53 (100.0)	
		Pain history (Year)		
= <1	6 (50.0)	6 (50.0)	12 (100.0)	
1-2	5 (35.7)	9 (64.3)	14 (100.0)	
2-3	8 (50.0)	8 (50.0)	16 (100.0)	0.494*
3-4	3 (37.5)	5 (62.5)	8 (100.0)	
= > 5	13 (65.0)	7 (35.0)	20 (100.0)	
		K-L XR knee score (Grade)		
II	14 (50.0)	14 (50.0)	28 (100.0)	
III	10 (50.0)	10 (50.0)	20 (100.0)	>
IV	11 (50.0)	11 (50.0)	22 (100.0)	0.99*

*Exact fisher test

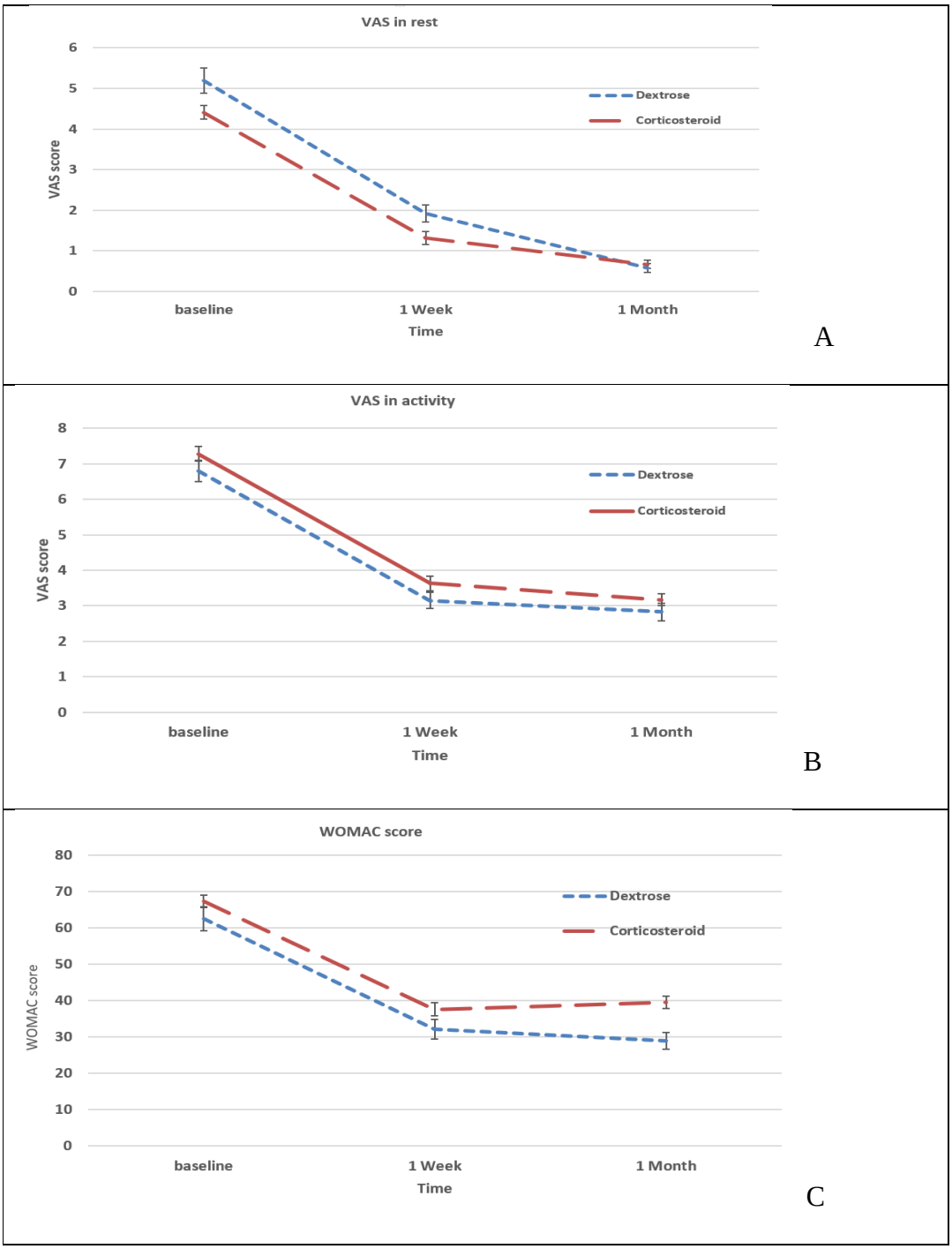

Figure 1. Mean change of pain and activity scores in knee osteoarthritis during the study of comparing early effects of Intra-articular hypertonic dextrose & corticosteroids.

Discussion

In the present study, we aimed to compare the early effects of HTD and CS injection in the arthritic knee and found that both intra-knee injection of single dose HTD 20% 5cc and triamcinolone 40mg significantly decreased both the rest and activity pain of KO one week and one month after the injection. There is no significant difference in the reducing effects of the two drugs. We also found that both injectates notably improve knee activity one week and one month after intervention, so the activity improvement effects with HTD were significantly more than triamcinolone. Also,

Table 2: Mean change of pain and activity scores in knee osteoarthritis during the study of comparing early effects of Intra-articular hypertonic dextrose & corticosteroids.

variable	group	Baseline	one week	one month	P-value*	P-value$
Rest VAS	**HTD**	5.20±1.70	1.91±1.15	0.57±0.61	0.235	<0.001
	CS	4.41±0.91	1.31±0.90	0.66±0.64		
	Total	4.81±1.42	1.61±1.07	0.61±0.62		0.058
Activity VAS	**HTD**	6.80±1.72	3.15±1.25	2.83±1.37	0.285	<0.001
	CS	7.28±1.20	3.63±1.13	3.17±0.98		
	Total	7.04±1.49	3.39±1.22	3.01±1.20		0.361
WOMAC score	**HTD**	62.54±18.32	32.23±14.82	29.03±12.83	<0.001	0.050
	CS	67.43±9.50	37.66±10.45	39.57±9.85		
	Total	64.98±14.69	34.94±13.02	34.30±21.58		0.074

*p-value between group; adj. baseline value of BMI & time; Linear mixed model analysis. $p-value within group; adj. BMI; repeated measure analysis

Table 3: Correlation coefficients of covariates in linear mixed model during the study of comparing early effects of Intra-articular hypertonic dextrose & corticosteroids on pain and activity scores in knee osteoarthritis.

variable	Dextrose	time	BMI	Baseline
VAS in rest	β=-0.19(0.16) p=0.235	β=-0.99(0.11) p<0.001	β=0.04(0.03) p=0.229	β=0.20(0.05) p<0.001
VAS in activity	β=-0.21(0.2) p=0.285	β=-0.39(0.11) p<0.001	β=0.03(0.04) p=0.490	β=0.56(0.06) p<0.001
WOMAC	β=-8.38(2.21) p<0.001	β=-0.64(0.75) p=0.392	β=0.19(0.44) p=0.654	β=0.53(0.07) p<0.001

Table 4: Comparison effects of Intra-articular hypertonic dextrose & corticosteroids on the satisfaction level in knee osteoarthritis patients.

Level of satisfaction	HTD	CS	Total
Moderate (to 50%)	2(66.7)	1(33.3)	3(100)
Strong (to 70%)	21(55.3)	17(44.7)	38(100)
Near Complete (to 90%)	12(41.4)	17(58.6)	29(100)
--	35(100)	35(100)	0.488*

*p-value

after one month of treatment, most participants in both groups were relatively satisfied with the intervention results. The rate of infection and hematoma after injection was zero in both groups. These findings are in line with the results of previous studies.

Hassan Fadi et al., in a systematic review of ten studies in 2017, Informed that knee prolotherapy has a significant effect in reducing pain, increasing range of motion, and improving performance and satisfaction of 80% of patients both in the short and long term (4 to 52 weeks)[29]. Ghasemi et al. in a RCT comparing intra-articular knee injection of HTD 15% and HTD 25% in

2017, found that pain and activity in both groups, especially the second group, significantly improved during the 1st to ninth week after injection[30].

Nasiri et al. in 2021 and Jahangiri et al. in 2014, in separate RCTs that compared CS and HTD effects on chronic inflammation of the rotator cuff and first carpometacarpal osteoarthritis (CMC1OA), respectively, both showed the effectiveness of HTD in short- term (3-4 weeks) and long-term periods. They concluded: prolotherapy may be a safe alternative therapy instead of IKCS due to lack of its side effects[31,32].

Islamian et al. in 2015, conducted a single-arm study with six-month follow-up in moderate KO. They found that by intra-articular injection of dextrose 20% 8cc, the mean values of rest VAS score, activity VAS score, and total WOMAC score decreased by 30%-40% compared to the baseline after one week[33].

This study chose a method of intra-articular injection and 20% dextrose concentration. In many studies, this method is effective in significantly reducing the symptoms of pain, stiffness, and movement limitation caused by KO. The possible responsible mechanism is the restoration of articular cartilage, subchondral bone, and hyaline membrane[34], also anti-nociception. As a result, positive changes in the knee radiographic appearance after injection have also been reported. In addition, a concentration of 20 to 25% has been introduced for this method[35].

Our study is the first that compared the effects of HTD with CS on KO in the one-week and the one month after injection, and similar to the studies above, the results showed that dextrose 20% is as effective as CS or more in improving pain and activity scores. Studies that have introduced HTD is less effective than CS in the short term have used HTD concentrations of less than 20%[36,37]. The strength of this study was that all injections were performed under ultrasound guidance, which increases the accuracy of intra-articular injection to 95%-100%[38]. Our study's limitation is the few samples and the single-blinding. IRCTs with a larger sample size and double or triple blinding are needed for much confirmation.

Conclusion

The early analgesic and activity-improvement effects of dextrose 20% in KO are comparable to CS. Intra-articular injection of HTD, as a well-known safe and inexpensive intervention with long-lasting regenerative effects, also can be introduced as a CS alternative treatment for early control of KO symptoms.

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Conflict of interest

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

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