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A Comparative Study of Short-Term Efficacy of Intra-articular Hypertonic Saline and Hypertonic Dextrose Prolotherapy in Knee Osteoarthritis: A Randomized Controlled Trial (RCT)

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ABSTRACT

Background: Knee osteoarthritis (KOA) is a common public health disease with an increasing prevalence. It is one of the leading causes of disability, especially in the elderly. Intra-articular hypertonic dextrose prolotherapy is one of the therapies used for KOA. There have been some articles indicating that patients receiving intra-articular normal saline as a control group of the article had improvement as well. The aim of this randomized clinical trial study was to evaluate the efficacy of intra-articular hypertonic saline in comparison with hypertonic dextrose prolotherapy in treatment of KOA.
Methods: A total of 54 patients with KOA were randomized in two groups: hypertonic dextrose (28 patients) and hypertonic saline groups (26 patients). All patients received three intra-articular injections of either hypertonic dextrose or hypertonic saline at two weeks intervals. The values obtained by visual analogue pain scale (VAS), Oxford knee scale (OKS), and Western Ontario McMaster University Osteoarthritis Index (WOMAC) questionnaire were the outcome measures which were evaluated before, as well as 2 and 4 weeks after the injections. The data were analyzed using t-test and repeated measurement tests.
Results: Both groups revealed improvements in outcome measures after 2 and 4 weeks of intervention. However, no statistically significant difference was found between the two groups.
Conclusion: We concluded that the intra-articular injection of hypertonic dextrose and hypertonic saline are both effective in the management of KOA. Hypertonic saline can be considered as another medical agent in management of KOA. However, further studies are suggested to evaluate its long-term effects.

Introduction

Knee osteoarthritis (KOA) is one of the common diseases with detrimental effects of movability, especially in the elderly. Pain and stiffness are the most common symptoms of the disease which compel the patient to seek treatment [1, 2]. Although many pharmacological and non-pharmacological treatments have been proposed, safe and effective management is still one of the research priorities [1]. Intra-articular and peri-articular injection in the knee is one of the treatments that can be proposed for KOA. Many substances such as platelet rich plasma (PRP), hyaluronic acid, methylprednisolone, human platelet lysate, etc. are used for intra-articular knee

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injections [3-5].

Prolotherapy has been used for over 80 years in musculoskeletal problems and pain conditions. It 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 adjacent joint space [1, 6]. The most common solution used in KOA prolotherapy is hypertonic dextrose which is injected in 12.5% up to 25% concentration. The exact mechanism of the prolotherapy agent in in-vivo environment is not completely understood [6]. It is proposed that hypertonic dextrose initiates an inflammatory cascade which promotes the release of growth factors and cytokines by dehydrating the cells. Thereafter, collagen production and cell proliferation are stimulated and culminate in reduction of pain and stiffness as well as strengthening of the connective tissue [2, 6, 7]. Further, many investigators have proposed that needle trauma and volume expansion of the tissue are effective and can also stimulate the inflammatory effect [7-9].

Furthermore, some studies have reported that patients in the normal saline groups had improvement as well in comparison to the dextrose one [10-13]. Thus, sodium chloride saline and even hypertonic saline can be another choice of treatment solution. It is water-soluble, has a normal blood chemistry component, and can be used in large volumes, as well. Although many studies have been performed using dextrose, no research has been done on the hypertonic saline.

Thus, the authors conducted this two-arm short-term RCT to determine whether hypertonic sodium chloride saline (2.5% concentration) can be effective or not.

Methods

Patients: This is a double-blinded, two-arm short-term randomized clinical trial (RCT) with a registry number of IRCT2016122931458N1. The research was conducted in public physical medicine and rehabilitation clinics in 2016-2017. The participants' enrollment was done by a general physician. Participants consisted of patients aged 40-70 years who met clinical criteria of knee osteoarthritis defined by American college rheumatology [3] and grade 2 or 3 Kellgren and Lawrence [14], and complained of pain and stiffness for at least one month.

Exclusion criteria: The following were the exclusion criteria:

Diabetes mellitus, pregnancy, rheumatologic or inflammatory diseases involving the knee joint, previous arthroplasty, intra-articular or peri-articular injection in the past three months, and body mass index (BMI) more than 42.

Randomization and allocation: After applying the exclusion criteria, 54 subjects were randomized by a computer random number system into two parallel groups (dextrose and saline groups). The patients and physician were blinded to the group randomization and allocation.

Intervention: The intra-articular injection was performed in three sessions with a two-week interval for each group. Injection in each group was performed by a physiatrist who was blinded to the syringe content. In the dextrose group, 3 ml of dextrose with 50% concentration was diluted with 3 ml of lidocaine 2%, while in the saline group 3 ml of saline with 5% concentration was diluted with 3 ml of lidocaine 2%. After injections, the patients were advised to place ice pack on the injection site for 5 minutes three times a day for 2 days and have relative knee rest for 3 days. They were recommended not to use non-steroid anti-inflammatory and other KOA therapies in the trial. They also were trained to have an appropriate lifestyle.

Outcome measures: The Oxford knee scale (OKS), Western Ontario and McMaster Universities arthritis index (WOMAC), and the visual analogue scale (VAS), questionnaire were filled out for each patient before the first injection as well as two and four weeks after the last injection. The VAS questionnaire was used to evaluate the pain intensity, where 0 and 10 represent no pain and the worst pain, respectively. The WOMAC questionnaire assessed three aspects of KOA including pain, stiffness, and physical function. The outcome of this questionnaire was 5, 2, 17 items for pain, stiffness, physical function. The OKS had 12 questions evaluating different aspects of KOA. In both OKS and WOMAC, each question had 0 to 5 score.

Statistics: The sample size for this study was extracted by sample size calculator program where the significance level, power, and probable dropout were 95%, 80% and 20%, respectively. Accordingly, the sample size for each group was estimated 30 patients.

The mean change in each outcome measure, between intra- and inter-groups, was analyzed by t-test and repeated measurement test. P-values less than 0.05 were considered significant. The Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago, IL, USA) was utilized for all analyses.

The ethics committee accepted this study with the reference number of IR.SUMS.MED.REC.1395.51. Participation in the trial was voluntary and informed consent was attained from individual participant after describing the RCT. The patients had the choice to leave the trial at any time they desired.

Results

About 60 subjects met the initial criteria; two participants declined to be in the RCT. After applying the exclusion criteria, 54 patients were enrolled in the trial and randomized. Specifically, 28 subjects were allocated in the dextrose group and 26 in the hypertonic saline group. However, after injection, four patients from the dextrose group and four from the hypertonic saline group did not attend the follow-up. At last, 24 participants in the dextrose and 23 in the hypertonic saline groups underwent analysis, as displayed in Figure 1.

No statistical differences were observed regarding reference characteristics between the groups, as reported in Table 1. The injection was done for each participant. The patients reported no adverse effect in the next visit, and no drug was consumed other than acetaminophen which was taken occasionally.

The mean VAS score in both hypertonic saline and

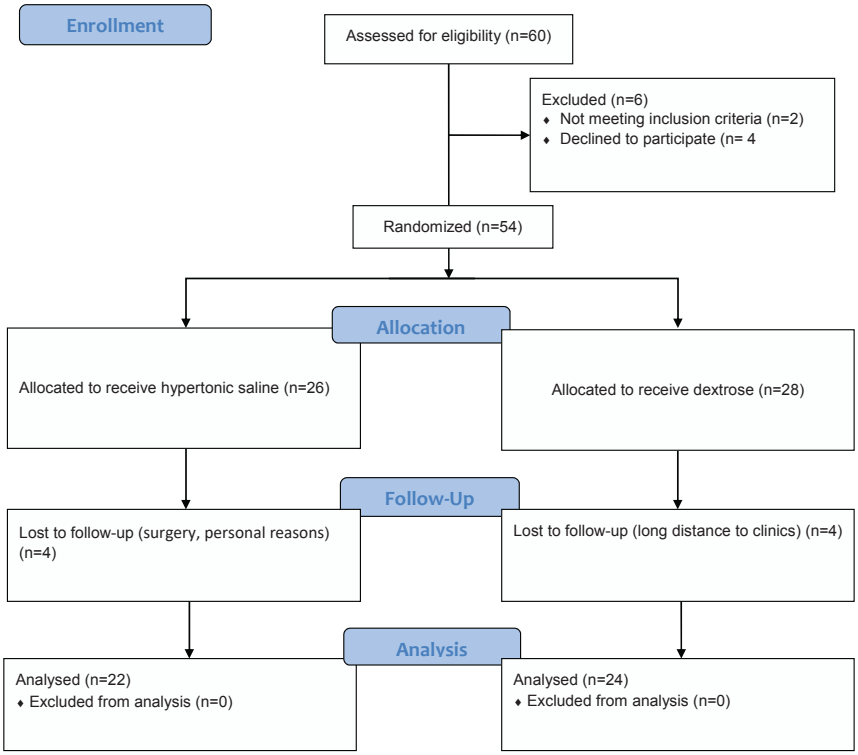

Figure 1: Consort flowchart

Table 1: The patients' reference characteristics

Characteristic		Dextrose (Mean±SD)	Saline (Mean±SD)	P value
Age (y)		60.16±9.07	57.45±10	0.34
Weight (Kg)		68.21±11.59	66.23±7.87	0.5
BMI (Kg/ m2)		26.87±3.81	26.42±2.89	0.65
Gender	Male	5	3	0.52
	Female	19	19	
VAS score (baseline)		77.5±19.83	83.18±14.6	0.27
OXFORD score (baseline)		20.29±7.6	19.2±6.5	0.61
WOMAC (baseline)	Pain	0.51±12	0.54±0.17	0.54
	Stiffness	0.45±0.22	0.52±0.26	0.28
	Physical function	0.53±0.09	0.58±0.17	0.12
	Total	0.52±0.09	0.56±0.14	0.17

BMI: body mass index, SD: standard deviation, WOMAC: Western Ontario and McMaster universities arthritis index, VAS: visual analogue scale

dextrose groups showed decrement over time, but it was not statistically significant between the two groups as listed in Table 2.

The OKS indicated a significant improvement between baseline and follow-ups after injection in both groups. However, it was not statistically significant between the patients who received hypertonic saline and dextrose injections (Tables 2 and 3).

The WOMAC total score revealed improvement in both dextrose and hypertonic saline groups. Although the decrement was greater in the hypertonic saline group over four weeks, there was no statistically significant difference between the two groups was observed (Table 4). The decline in all aspects of WOMAC questionnaire including pain, stiffness, and function was seen over four weeks in both groups, but it showed no significant differences (Table 4).

Discussion

The prolotherapy is one of the interventions introduced for different musculoskeletal conditions. It is safe and

Table 2: Comparison between visual analogue scale (VAS) and Oxford knee scale (OKS) score changes in the dextrose and hypertonic saline groups

Scale		Dextrose (Mean±SD)	Hypertonic saline (Mean±SD)
VAS	Baseline	77.5±19.83	83.18±14.6
	2 weeks	71.04±20.4	75.45±18.9
	4 weeks	68.17±19.9	70±18.52
OKS	Baseline	20.29±7.6	19.2±6.5
	2 weeks	21.12±7.8	21.59±6.6
	4 weeks	21.54±7.8	24.45±7.2

SD: standard deviation, VAS: visual analogue scale, OKS: Oxford knee scale

Table 3: Improvement in Oxford questionnaire grading of knee osteoarthritis (KOA)

Group		Grade 1 (0-19)	Grade 2 (20-29)	Grade 3 (30-39)	Grade 4 (40-48)	P value
Dextrose	Baseline	50%	37.5%	12.5%	0	>0.05
	2 weeks	41.7%	41.7%	16.7%	0	
	4 weeks	41.7%	41.7%	16.7%	0	
Hypertonic saline	Baseline	36.6%	31.8%	0	4.5%	<0.05
	2 weeks	45.5%	50%	0	4.5%	
	4 weeks	22.7%	63.6%	9.1%	4.5%	

Table 4: Evaluation of Western Ontario and McMaster Universities arthritis index (WOMAC) and its subscales in the two groups

Variable		Dextrose (Mean±SD)	Hypertonic saline (Mean±SD)
Total WOMAC	Baseline	0.52±0.09	0.56±0.14
	2 weeks	0.5±0.11	0.47±0.14
	4 weeks	0.5±0.12	0.47±0.16
Pain	Baseline	0.51±0.12	0.54±0.17
	2 weeks	0.49±0.12	0.48±0.18
	4 weeks	0.48±0.13	0.44±0.18
Stiffness	Baseline	0.45±0.22	0.52±0.26
	2 weeks	0.45±0.22	0.47±0.23
	4 weeks	0.44±0.22	0.47±0.23
Function	Baseline	0.53±0.09	0.58±0.13
	2 weeks	0.5±0.11	0.51±0.13
	4 weeks	0.5±0.11	0.51±0.15

SD: standard deviation, McMaster universities arthritis index and, WOMAC: Western Ontario.

inexpensive in comparison to other intra-articular injections, such as PRP, hyaluronic acid, and human platelet lysate. Some studies have reported that patients in the RCT who received normal saline also showed improvements [10, 15, 16]. In the literature, there are several reports that show and prove the great efficacy of prolotherapy with hypertonic dextrose compared to placebo group such as normal saline [17]. Hence, the authors decided to consider prolotherapy with hypertonic dextrose as a well-known method to evaluate the effectiveness of hypertonic saline. Thus, in this research, the effectiveness of hypertonic saline in comparison to dextrose was investigated. This RCT revealed that hypertonic saline could improve the KOA symptoms in a short time as well. The authors also showed that VAS score was reduced in both dextrose and hypertonic saline groups. In the research conducted by Rabago et al., the patients with KOA underwent either prolotherapy or normal saline injections. After 52 weeks, all groups reported improved WOMAC compared to the baseline, which is in line with our result of WOMAC score. However, the prolotherapy group revealed a significant score adjusted for age and gender [12]. In Yelland et al.'s study, prolotherapy with dextrose and normal saline was compared in chronic low back pain. In this study, both the prolotherapy and normal saline groups indicated a statistically significant reduction in VAS and disability scores [10].

In another study, 10% dextrose versus normal saline was used in temporomandibular joint (TMJ) pain. After two injections with an interval of six weeks, both dextrose and placebo groups showed significant improvements in TMJ pain and locking [15]. Thus, normal saline had a positive effect on pain and even locking as dextrose. Also, in a meta-analysis study by B.M. Saltzman et al.[18], it was shown that for patients with knee OA, intra-articular normal saline injection yielded significant improvements in a six-month follow-up. In addition, in a study [19], it was demonstrated that intra-articular hypertonic saline injection was effective for pain reduction and improving function. These data were in line with our results.

In 2020, B. Tavana et al. investigated the effect of a single intra-articular knee joint injection of hypertonic saline on pain reduction and functional improvement in patients with moderate or moderate to severe KOA in a single arm study, and found its positive effectiveness [20]. Similarly, our study observed three sessions of intra-articular knee joint injection of hypertonic saline as efficacious as hypertonic dextrose in pain management of KOA.

This research demonstrated improvements in all three sections of WOMAC score, but it was more significant in the hypertonic saline. In two previous trials by Rabago et al., either dextrose or dextrose mixed with sodium morrhuate showed more improvements than normal saline, but it reached minimal clinically important difference (MCID) at 12 and 52 weeks of follow up [1, 8]. Thus, the differences in the results in this research might be due to the number of injection sessions, using both extra- and intra- articular injections, and duration of follow-ups.

Lack of the sham group was the main limitation of the study. Also, as this study had a short-term follow-up. To assess the definite effect of hypertonic saline, it is suggested that further research be done on larger sample size groups with a long-term follow-up.

Conclusion

The data revealed that hypertonic saline was as effective as dextrose in management of KOA in the short-term follow-up. As a significant improvement was

seen even two weeks after the injection of hypertonic saline, it can be considered as another medical agent for knee osteoarthritis pain management and life quality improvement. However, further investigation is required to evaluate the effect of hypertonic saline on the knee osteoarthritis in the long-term.

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Conflict of Interest: None declared.

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