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Efficacy of hypertonic dextrose (prolotherapy) in early knee osteoarthritis: a short term outcome

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ABSTRACT

Background: Knee osteoarthritis (OA) is a prevalent, painful, and progressive condition significantly affecting patients' quality of life and imposing a social and economic burden. Traditionally managed through symptom relief and joint function improvement, research is increasingly focusing on disease-modifying treatments. Dextrose prolotherapy, a low-cost alternative involving the injection of a hypertonic solution, has shown promise despite limited acceptance in current guidelines.
Methods: This prospective cohort study, approved by the Institutional Ethical Board of Jamia Hamdard University, assessed the effects of 12.5% hypertonic dextrose prolotherapy in 92 patients with knee OA. Patients received injections at multiple sites over a 6-week period. Outcomes were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and visual analog scale (VAS) scores at baseline, 4, 8, 16, and 24 weeks.
Results: Significant improvements were observed in both WOMAC and VAS scores. WOMAC scores decreased from 53.83 to 26.70 ($p<0.0001$), and VAS scores dropped from 7.12 to 3.06 ($p<0.0001$) at the 24-week follow-up. No major complications were noted, with minimal adverse effects reported. Improvement was consistent across all OA grades.
Conclusions: Dextrose prolotherapy demonstrated substantial, sustained improvements in pain and function in knee OA patients. Given its safety, low cost, and efficacy, it represents a viable therapeutic option, especially in resource-constrained settings. Further high-quality randomized controlled trials are needed to confirm these findings and optimize treatment protocols.

Keywords: Knee osteoarthritis, Dextrose prolotherapy, WOMAC, Visual analog scale, Pain management, Treatment efficacy

INTRODUCTION

Knee osteoarthritis (OA) is a common painful affliction of the knee joints which has a chronic and progressive course often resulting in a poor quality of life to the patients and significant social and economic burden. With a lifetime risk of symptomatic knee OA of 45%, it is a very common condition in the adult population.[1] While it was earlier considered to be a result of ageing process, ongoing research suggested that the pathogenesis of OA is more complex and multifactorial.[2] Treatments currently available are focused on symptom relief and improving joint function, rather than modifying the disease progression. These include non-pharmacological, pharmacological, and interventional procedures such as intra-articular corticosteroid or hyaluronic acid infiltrations.[3] However, ongoing research is looking at various disease-modifying treatments that aim to regulate cartilage catabolism and anabolism, inflammation control, and remodelling of subchondral bone.[4]

Various injection-based therapies have been investigated for knee OA in recent years, including dextrose prolotherapy, ozone, botulinum toxin, platelet-rich plasma, and hyaluronic acid.[5-8] Most of these treatments are expensive and have limited therapeutic efficacy for symptom control. Dextrose is a low-cost and widely available option in clinical settings, making it an attractive alternative for managing chronic painful musculoskeletal conditions. Prolotherapy has been used since the 1940s with increased interest in the 1990s.[9] Although the mechanism behind prolotherapy is not completely understood, it is believed that the initiation of a local inflammatory response leading to tissue proliferation and remodeling is involved in the healing process.[10]

Dextrose prolotherapy involves injecting an irritant hypertonic solution at multiple sites that correspond to painful tendons and ligament insertions or within the joint to initiate a healing response. Although there are numerous reports of clinical success with dextrose prolotherapy for musculoskeletal issues, it has not been widely accepted as a treatment for knee osteoarthritis in recent guidelines. The 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the hand, hip, and knee conditionally recommends against the use of prolotherapy in patients with knee OA.[11] Similarly the guidelines from the Osteoarthritis Research Society International (OARSI) advised against dextrose prolotherapy due to insufficient evidence of its effectiveness.[12] However there is growing interest in dextrose prolotherapy due to its high safety profile, low cost, short hospital stay, ease of administration, and potential therapeutic impact that may readily be conducted in the primary care context and is thus worth considering.[9,13] A growing body of literature, particularly in the last decade, suggests positive outcomes for various functional domains of osteoarthritis with the use of prolotherapy.[14,15]

The purpose of this study was to study the results and functional outcome of use of HDT/prolotherapy in patients with knee OA using validated scoring systems like Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and visual analog scale (VAS).

METHODS

This study was approved by Institutional Ethical Board of Hamdard Institute of Medical Science and Research, of Jamia Hamdard University, Delhi after seeking the approval from the Ethical Committee of Jamia University Ethical Board and then study was started. This was a prospective cohort study carried out between 01 September 2022 to 01 June 2023. The patients were recruited from the out-patient department of orthopaedics of HAHC Hospital. To evaluate the clinical and functional outcome of 12.5% hypertonic dextrose injection in the treatment of early osteoarthritis knee based on WOMAC scale and VAS, we included adults aged more than 40 years with complaints of pain and stiffness in the knee, of more than 3 months duration with X-ray suggestive of OA in our study as per the Kellgren-Lawrence grading. We included 92 patients in this study, recruited from the outpatient department of orthopaedics, HAHC hospital.

Eligibility

All patients between 40 and 75 years of age with clinical and radiographic diagnosis of knee osteoarthritis (KOA) as per the American College of Rheumatologists criteria on a recent X-ray of knee were assessed for eligibility in the study.[16]

Inclusion criteria

Knee OA grade I, II and III as per Kellgren-Lawrence grading system were included. Patients who reported moderate to severe knee pain for at least 3 months, defined as a score of ≥3 (moderate or more) based on VAS score, tenderness of 1 or more anterior knee structures on physical examination, and who failed to achieve pain reduction to a score <3 (on VAS) after 3 months of usual care, such as weight reduction, exercise, physical therapy and pharmacological treatment were also included.

Exclusion criteria

Exclusion criteria included pregnancy, uncontrolled diabetes, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, previous fracture around the knee, any knee injection within 3 months, inflammatory or post-infectious knee arthritis, daily use of opioid medication, allergy or intolerance to study medication, body mass index (BMI) greater than 40 kg/m^2, and comorbidity severe enough to prevent participation in the study protocol.

In cases with bilateral involvement only one knee was injected and included in the study. Interested, eligible persons were given information regarding the procedure, provided consent for participation, and were enrolled in the study.

Injection technique

Eighteen (18) milliliters of solution containing (9 ml of 25% dextrose + 9 ml of 2% lignocaine) was prepared and given at 6 extra-articular site (2 ml each) and one intra-articular injection (6ml) using infra-medial approach at the gap of 3 weeks. A total of three doses (week 0, week 3 and week 6) of injection were given in a single knee under all aseptic precautions.

After injection compression bandage was applied and the patient was advised for ice pack application for a day and the compression bandage was removed 24 hours later and physiotherapy was commenced as tolerated for quadriceps and hamstring strengthening exercises. Patients were allowed to take paracetamol for pain relief as and when

required. Patients were discouraged from using non-steroidal anti-inflammatory medications (NSAIDs) and from starting any new therapies for their osteoarthritis during the study period.

Extra-articular sites are: origin and insertion of MCL ligament, origin and insertion of LCL ligament, quadriceps tendon, and patellar tendon.

RESULTS

Our study encompassed a cohort of 92 patients, consisting of 58 females and 34 males. Among them, bilateral involvement was observed in 68 patients, while the remaining 24 patients exhibited unilateral involvement. Specifically, each patient received an injection in one knee, resulting in a total of 92 knees being examined.

Approximately 35% of the patients were classified as overweight, and around 37% fell into the obese category. The average age of our study population was 58.6 years, with male patients tending to be slightly older than their female counterparts (60.1 years versus 57.7 years). The duration of symptoms ranged from approximately 3 years to as long as 11 years, with an average duration of 7.8 years. Additionally, all knees were further classified based on the Kellgren and Lawrence grading system for osteoarthritis. The table depicts that the commonest presentation was grade II OA [n=43 (46.73%] followed by grade-3 [n=29 (31.52%] and grade-1 [n=20 (21.73%], respectively (Table 1).

Table 1: Demographic and clinical characteristics at baseline.

Characteristics	N (%)
Age (years)	
Mean	58.6
Male	60.1
Female	57.7
Body mass index	
Underweight <18.5	03
Normal 18.5-22.9	23
Over-weight 23-24.9	32
Obese >25	34
Sex (%)	
Male	34 (37)
Female	58 (63)
Duration of symptoms (y)	7.8
OA grade (Kellgren-Lawrence) (%)	
1	20 (21.73)
2	43 (46.73)
3	29 (31.52)
4	0
Knee pain (VAS)	7.120
WOMAC score	53.83

In all patients, a baseline mean score for WOMAC and VAS was initially calculated using statistical package for the social sciences (SPSS). This same scoring system was employed to track and evaluate the patients' response during subsequent follow-up visits. The duration of each follow-up visit was measured from the date of the initial injection.

Throughout the follow-up period, which included visits at 4, 8, 16, and 24 weeks, we consistently observed a progressive improvement in the scores. Notably, the mean WOMAC score demonstrated a significant enhancement, decreasing from a baseline value of 53.83±7.99 to 26.70±7.74 at the 24-week mark.

The study group's mean WOMAC score exhibited a gradual decrease at different follow-up visits compared to the baseline, and this reduction was statistically significant ($p<0.0001$) (Figure 1).

Likewise, the mean VAS scores demonstrated consistent improvement throughout the various follow-up visits. Specifically, the mean VAS score decreased from a baseline of 7.12±1.17 to 3.06±1.47 at the final 24-week follow-up visit. This improvement was also found to be statistically significant ($p<0.0001$).

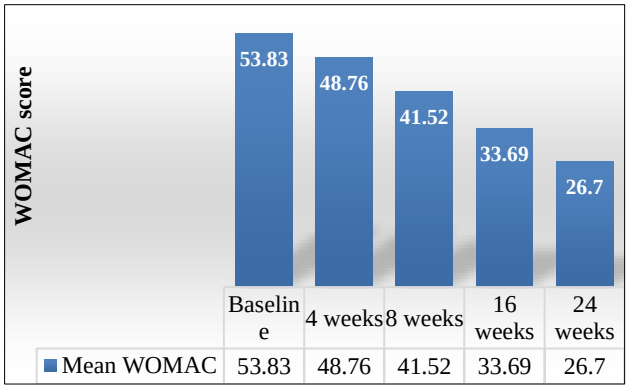

Figure 1: Graphical presentation of comparison of mean WOMAC score.

Patients' mean VAS scores showed a gradual improvement at follow-up visits compared to the baseline, and this difference was found to be statistically significant ($p<0.0001$) (Figure 2).

Furthermore, a statistical analysis comparing the mean WOMAC scores in relation to the Kellgren and Lawrence (KL) grade of osteoarthritis (OA) demonstrated the beneficial effects of prolotherapy in all stages of knee OA. While the baseline mean WOMAC scores were understandably worse with increasing grades (I, II, and III), patients in all grades exhibited progressive and statistically significant improvement in their mean WOMAC scores at each follow-up visit (Table 2).

Table 2: Tabular presentation of mean of comparison of WOMAC score versus grade of OA in included patients.

WOMAC versus OA GRADE	Baseline		4 weeks		8 weeks		16 weeks		24 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	47.14	7.19	41.29	7.14	33.37	7.54	28.49	7.21	22.24	7.32
2	55.23	6.33	50.49	6.34	43.81	6.43	30.96	6.69	23.43	6.71
3	58.38	5.14	53.57	5.00	46.67	5.46	37.57	5.29	34.14	5.10
P value	F=103.5 P<0.0001*		F=37.19 P<0.0001*		F=41.87 P<0.0001*		F=18.25 P<0.0001*		F=17.01 P<0.0001*	

*Significant

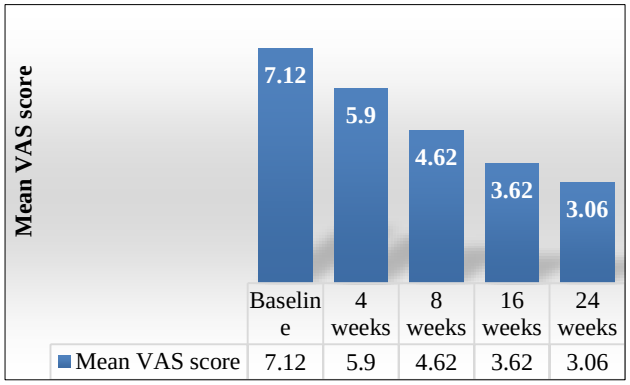

Figure 2: Graphical presentation of comparison of mean VAS score.

During the study, no significant complications such as infection, hemarthrosis, or neurovascular complications were observed among the patients. However, it is worth noting that two patients reported experiencing intractable pain that persisted even after the injections were administered (Table 3).

Table 3: Tabular presentation of complications in patients.

Complications (beyond >72 hours)	Number	Percentage
Intractable pain	2	2.17
Swelling	0	0.00
Infection	0	0.00
Bleeding/haemarthrosis	0	0.00
Neurovascular	0	0.00
Redness/skin discoloration	0	0.00

DISCUSSION

The current study of adults with symptomatic knee osteoarthritis found substantial, consistent and significant improvement in pain and range of motion according to WOMAC and VAS score. Furthermore, the treatment was highly cost-effective, which is particularly beneficial for resource-poor countries like ours. The average expense for each session at our hospital amounted to approximately 1000 INR (equivalent to around 12 USD).

The authors of a systematic review by Sit et al concluded that dextrose prolotherapy was significantly beneficial in treating symptomatic knee osteoarthritis (OA).[17] Another systematic review evaluated ten studies and found moderate evidence to suggest that dextrose prolotherapy was safe and could help achieve significant symptomatic control in patients with knee OA.[18] A 2019 systematic review reported statistically significant outcomes for dextrose prolotherapy in knee OA with positive functional and pain outcomes.[8] Several studies with a significant number of participants have shown a favorable outcome for dextrose prolotherapy compared to other treatments; however, these studies also discussed alternative treatment options.[17,19-22] Like the current study, most other studies commonly used the WOMAC and VAS as outcome measures, but one study reported objective outcome measures such as performance tests like 30 second chair stand test, 40 meter fast-paced walk test, and timed-up-and-go test.[17]

No major complications were observed in the current study but we witnessed some minor complications (persistent intractable pain) in 2 of our patients. According to many studies and systematic reviews, patients who received HDP did not experience any side effects or adverse reactions.[8,15,18,23-26] In contrast, two other studies reported minimal adverse reactions in both the HDP-treated groups and control groups, such as mild to moderate pain, inflammation, and self-limiting hematomas.[27,28]

Dosage

According to a systematic review, the dosages used for hypertonic dextrose prolotherapy (HDP) in treating knee osteoarthritis (OA) varied widely, with patients receiving 1 to 5 doses and a mode of 3 doses.[8] Wee et al found most studies favored a three-injection regime, many authors using dextrose solutions of less than 20% and others used between 20% and 25% dextrose solutions. However, there was a lack of consistency in clinical trials or practice regarding the intervals between injections, which ranged from a single injection to weekly, monthly, or bimonthly with monthly applications being the most commonly used.[29] Intra-articular injections typically used dextrose concentrations ranging from 10% to 25%, with 25% being the most frequently used concentration, and a volume of 2 to 8 ml per application. Extra-articular injections involved a 15% concentration and were applied to tendon and ligament insertion points, pain points, and points corresponding to the emerging knee superficial sensory nerves. The authors recommend a dosage of 2 to 6 sessions

of prolotherapy at monthly intervals, using dextrose concentrations of 25% for intra-articular injections and 15% for extra-joint sites.[14] The current study used 3 injections of 12.5% of dextrose given in intraarticular and extraarticular locations at interval of three weeks between the injections.

Mechanism of action of HDP

Although the mechanism of action of prolotherapy is unknown, multiple hypotheses have been proposed. It is believed to produce a pro-inflammatory response that leads to the production of growth factors and cytokines, ultimately culminating in the regeneration process in the affected joint which drives local repair of wounded extra- and intra-articular tissue.[27]

Research has shown that even a slight increase in extracellular glucose levels to 0.5% can elevate polypeptide growth factor levels in human cells.[30-34] Additionally, exposure to a hypertonic environment can also quickly increase DNA levels for growth factors within seconds to minutes.[9,35] By these two mechanisms for increasing growth factors, HDP potentially benefits critical cells in the joint, such as chondrocytes, osteocytes, and fibroblasts. In addition to dextrose-specific effects, needle trauma and volume expansion of local tissue may also produce tissue-level effects in regeneration of the damaged articular cartilage and thus help in combat the pain felt by the patient in normal day to day activities.[36]

Hypertonic dextrose solution offers both short-term and long-term analgesic effects in prolotherapy. Short-term analgesia is achieved through neurogenic mechanisms, such as hyperpolarization of nerve fibers by opening potassium channels or stimulation of the glycine inhibitory receptor, which reduces nociceptive transmission.[37,38] Long-term analgesia is achieved through the repair of soft tissues and cartilage.[39] Additionally, a recent study reported that glucose decreased the expression of metalloproteinase 1.[40] Topol et al through a histological evaluation, reported that hypertonic dextrose application had chondrogenic effects and induced the healing process at the expense of hyaline cartilage and fibrocartilage formation; while Reeves et al reported a decrease in ligamentous laxity in patients with anterior cruciate ligament involvement when treated with hypertonic dextrose.[27,39]

Furthermore, hypertonic solutions are considered to function by blocking transient receptor potential vanilloid type 1, a membrane cation channel that enables the influx of Na^+ and Ca^{2+}. Sodium influx is considered to result in action potential and nociception, whereas calcium results in the production of substance P and calcitonin gene-related peptides. The inhibition of intake of both cations can theoretically lessen neuropathic pain, edema and tissue intramuscular compartment pressure. Peri-articular dextrose injection has also been demonstrated to improve healing in animals by promoting vascular and fibroblast proliferation and cartilage thickening.[27]

A systematic review highlights several unresolved questions regarding the periprocedural aspects of dextrose prolotherapy.[8] These questions pertain to the specific site of injection, the optimal concentration of dextrose, the number of injections required, and the interval between injections.

In three studies, hypertonic dextrose was utilized as a single intervention for intra-articular application.[25-27] Notably, all of these studies demonstrated a statistically significant reduction in pain and improvement in function for a duration of up to 6 months.

Several studies have compared the therapeutic effects of intra-articular hypertonic dextrose with subcutaneous dextrose and have found similar reduction of pain and function improvement, which may be due to neurogenic effects rather than chondrogenic mechanisms or ligamentous/tendinous remodeling.[26] Additionally, two studies that combined intra-articular and extra-articular HDP applications on ligament insertions and tendons observed a long-term effect, which could be explained by a probable summative effect of the various mechanisms mentioned above.[24,28]

According to previous systematic reviews and meta-analyses, hypertonic dextrose prolotherapy (HDP) may have a greater effect on reducing pain and improving function in patients with knee OA.[17] However, these reviews included case series studies in their analysis and/or compared HDP with non-interventional treatments or placebo injections. Nine studies examined long-term effects of HDP with a follow-up of 2-3 months, all of which reported sustained benefits. Four studies evaluated HDP effects at 5-6 months, with three of them reporting continued effectiveness.[24,26,28] Two studies evaluated HDP effects at 12 months and found that the benefits persisted throughout the year.[24,28] In addition, case series studies by Rabago et al also observed long lasting effects, one of which monitored patients for 2.5 years and reported persisting benefits.[33] These findings suggest that HDP may provide long-term benefits that outlast those of corticosteroids, hyaluronic acid, and ozone, and are comparable to the effects of platelet-rich plasma treatment. Nevertheless, more studies with long-term follow-ups are necessary to confirm these observations.

Determination of clinical utility of prolotherapy will require confirmation in a larger effectiveness trial that includes biomechanical and imaging outcome measures to assess potential disease modification. Clinical trials designed to optimize dose and assess biological mechanism of action are also warranted.

The findings of the current study suggest that dextrose prolotherapy may improve upon standard care of knee osteoarthritis for certain patients. Its use in clinical practice

is relatively uncomplicated; the procedure is simple to learn, easy to administer, is performed in the outpatient setting without ultrasound guidance, takes around 15 minutes for a procedure, and is very cost effective which makes it an attractive therapeutic modality in resource poor countries.

Limitations

Though being such benefical modality of treatment for osteoarthritis this study has some limitations too which include a relatively small sample size, though the effect size of prolotherapy proved adequate relief on our scoring system. The study was not large enough to detect uncommon adverse events, such as intolerance to study medication or rare injection-related sequelae. A lack of control group or a 'usual care' group also limits the external validity of the results. The exclusion of patients taking chronic opioids and morbidly obese patients (BMI >40 kg/m^2) may limit the generalizability of the results, safety of this modality on people suffering from diabetes mellitus. While the study monitored pharmacologic interventions during the follow-up period, limited data was collected regarding the extent of exercise and weight loss in each group, which may have influenced the outcomes.

CONCLUSION

The findings of this study provide compelling evidence that HDP is an effective treatment for knee OA, offering both significant and sustained improvements in patient outcomes. The use of HDP resulted in notable reductions in pain, as indicated by the VAS, and improvements in functional status, as measured by the WOMAC. These benefits were observed across various grades of OA, suggesting that HDP is a versatile treatment option. The study's results align with recent literature that supports the potential of HDP to provide durable benefits comparable to or exceeding other available treatments. Despite some limitations, such as the lack of a control group and the relatively small sample size, the study underscores the potential of HDP as a cost-effective, low-risk intervention that could be particularly beneficial in resource-limited settings. This research advances our understanding of dextrose prolotherapy by demonstrating its practical application and effectiveness in real-world clinical settings. Future studies should aim to further elucidate the mechanism of action and optimize treatment protocols to maximize patient benefits.

Recommendations

Conduct larger and multi-center trials

To validate the efficacy and safety of dextrose prolotherapy, it is essential to conduct larger-scale studies involving diverse patient populations across multiple centers. This will help to generalize the findings and confirm the results observed in this study.

Standardize treatment protocols

Future research should focus on standardizing the treatment protocols for HDP, including the concentration of dextrose, the volume of injections, and the frequency of administration. This will facilitate more consistent results and allow for better comparison between studies.

Assess combination therapies

Future research should explore the efficacy of HDP in combination with other treatment modalities, such as physical therapy or pharmacological agents, to determine if combined approaches offer superior outcomes for patients with knee OA.

Evaluate cost-effectiveness and accessibility

Given the promising results and low cost of HDP, studies evaluating its cost-effectiveness compared to other treatments and its accessibility in different healthcare settings should be conducted. This will help in making informed decisions about incorporating HDP into standard care practices.

By addressing these recommendations, the clinical utility of dextrose prolotherapy can be further established, and its role in the management of knee osteoarthritis can be better defined, ultimately leading to improved patient outcomes and more effective treatment strategies.

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