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# A RANDOMIZED CONTROLLED PLACEBO STUDY OF DEXTROSE IONTOPHORESIS VERSUS DEXTROSE PROLOTHERAPY IN CASE OF KNEE OSTEOARTHRITIS

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## ABSTRACT

***Background:*** Osteoarthritis is the most common cause of musculoskeletal pain and disability in the knee joint. This study investigated the efficacy of Dextrose iontophoresis versus Dextrose prolotherapy in case of knee osteoarthritis in a randomized, placebo-controlled, double-blinded study.

***Methods:*** sixty patients diagnosed mild to moderate osteoarthritis were included in the study. Their age's were45:65 years with mean age 51 ± 3.5 years. Patients were divided randomly into three equal groups, group (A)received 50 % dextrose iontophoresis, group (B) Each patient received three intra-articular injections of dextrose at 1-month intervals in weeks 0, 4, and 8 and group (C ) received sham iontophoresis. The outcome measurements were Western Ontario and McMaster Universities arthritis index (WOMAC) values, knee ROM, and pain severity at rest (seated) and in activity (after walking 6 m) using the visual analogue scale (VAS) were recorded. The patients were evaluated for these parameters before allocated in their groups then after 4, 8, and 24 weeks later.

***Results:*** compared to sham group (placebo) there were significant improvement of VAS and ROM of iontophoresis group than sham (placebo) group ($p < 0.000$). Also there were significant improvement of prolotherapy group than placebo ($p < 0.006$, and 0.02) respectively. Furthermore there was significant improve of iontophoresis group than prolotherapy where p was $< 0.000$ for VAS, ROM and (WOMAC).

***Conclusion:*** The results of this study suggested that both dextrose iontophoresis and dextrose prolotherapy may be as useful modalities in treatment of osteoarthritis with better effects of dextrose iontophoresis than prolotherapy.

***Keywords:*** dextrose, prolotherapy, iontophoresis, knee osteoarthritis, range of motion, intra-articular injections.

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## INTRODUCTION

Osteoarthritis (OA) is an age-dependent disease caused by degenerative and healing processes in subchondral tissue of articular and bone cartilage, resulting in an alteration of its biomechanical properties that eventually causes pain, stiffness, and decreased articular function.[1]

"osteo", meaning "of the bone", "arthro", meaning "joint", and "it is", meaning inflammation, although the "it is" of osteoarthritis is somewhat of a misnomer – inflammation is not a conspicuous feature which is present in rheumatoid or autoimmune types of arthritis. Some clinicians refer to this condition as osteoarthrosis to signify the lack of inflammatory response.[2]

Osteoarthritis traditionally was considered as a disease of articular cartilage. Now it is thought to involve the entire joint tissues, synovium, capsule, bone and ligaments leading to subchondral bone attrition and remodelling, meniscal degeneration, ligamentous laxity, fat pad extrusion, and impairments of neuromuscular control. The cartilage is poorly innervated and is not the cause of pain. The diagnosis must be made clinically because laboratory test may not be helpful and radiological findings do not necessarily correlate with the symptoms.[3]

OA knee increases with age (older than 50 years), especially in women. According to a number of published reports, anywhere from 6% to over 13% of men, but between 7% and 19% of women, over 45 years of age are affected, resulting in a 45% less risk of incidence in men (4). Additional factors that increase the risk of developing OA of the knee include genetics and obesity.[5]

Genetic factors appear to influence risk of developing primary OA though they may influence disease differently in men and women. Twin studies suggest that generalised OA in women has a heritability rate of 39 to 65%, with a concordance rate in monozygotic twins of 0.64.[6, 7, 8]

### Signs and symptoms

Although any joint in the body can be affected by OA, the knee joint is more commonly involved especially in the Indian sub-continent. Pain is the first and predominant symptom, causing loss of ability and often stiffness. "Pain" is generally described as a sharp ache, or a burning sensation in the associated muscles and tendons. The pain is intermittent and is worse with use and better with rest.[9]

The stiffness generally improves after 30 minutes of activity unlike the prolonged (usually > 30 min) stiffness caused by rheumatoid arthritis. Humid and cold weather increases the pain in many patients. As OA progresses, the affected joints appear larger, are stiff and painful, and usually feel better with gentle use but worse with excessive or prolonged use, thus distinguishing it from rheumatoid arthritis. OA of the knee can cause a crackling noise called "crepitus", when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons. Occasionally, the patient presents with swelling or joint effusion.[10]

Iontophoresis is a technique which uses an electric current to deliver a medicine or other chemical through the skin. It is a non-invasive method of propelling high concentrations of a charged substance, (normally a medication or bioactive agent), transdermally by repulsive electromotive force using a small electrical charge applied to an iontophoresis chamber containing a similarly charged active agent and its vehicle". The term iontophoresis is simply defined as ion transfer (ionto = ion; phoresis = transfer).[11,12]

The penetration of the ions is greatest in the region of the pores; the penetration of the substance through the skin is in proportion to the current magnitude, but that the substance is most likely deposited below the stratum corneum, thus acting as a depot. Onward migration of the substance to the deeper tissues is achieved by diffusion rather than being 'driven' deeper by the applied current.[13]

In general terms, low current intensities appear to achieve favorable results. The treatment is usually applied with currents up to 5mA, It has been suggested that commonly, the NEGATIVE electrode is made larger (relative to the positive electrode) to avoid skin irritation (whether the ionic driving electrode or not).[14]

Dextrose Prolotherapy for Knee Osteoarthritis is one of most recent approach in dealing with OA, Prolotherapy is an injection therapy for chronic musculoskeletal injury, including knee osteoarthritis. A core principle is the injection of small volumes of an irritant solution at multiple painful ligament and tendon insertions and in adjacent joint spaces over several treatment sessions.[15]

Prolotherapy, also known as proliferative therapy, or regeneration injection therapy, is a complementary injection treatment for musculoskeletal pains. Hypertonic dextrose is the most commonly injected solution. Although the mechanism of this treatment modality is not clearly understood, it is hypothesized that the solution creates a host inflammatory response through the upgrading of chemical mediators,

which results in stronger connective tissue, improved biomechanics, and joint function and soft tissue recovery.[15]
Several reports have revealed the effects of dextrose prolotherapy in treating refractory musculoskeletal disorders such as low back pain, tendonitis, lateral epicondylitis, and ligament damage.[16]

There are few treatment methods for moderate to severe OA; most focus on relieving the symptoms but do little to change the biochemical environment of the joint or on the disease process. Current therapies include simple analgesics, anti-inflammatory drugs, muscle strengthening exercises, physical therapy, intra-articular injection of cartilage supplements such as hyaluronic acid agents, arthroscopic surgery, and arthroplasty nevertheless no nonsurgical treatment is uniformly effective.[17,18]

It should be noted that the number of elderly people in society is increasing and musculoskeletal disorders, mainly OA in this population, are very common. Routine treatments for pain and disability in these patients have low efficacy, and some treatments, including hyaluronic acid injection therapy, have high costs. It is possible that prolotherapy has acceptable effects on OA in these patients but it considers invasive methods due to hazards of injection.[16]

Therefore, we designed this study to investigate the effectiveness of dextrose iontophoresis versus dextrose polorotherapy in decreasing pain, improving daily functional ability, and increasing the joint range of motion (ROM) in patients with knee OA.

## METHODS AND MATERIALS

60 adult patients (50 female and 10 male) their ages were 45:65 years old with mean age 51 ± 3.5 year. Diagnosed with bilateral knee OA based on the clinical criteria of the American Rheumatological Association.[19] Who met the inclusion and exclusion criteria, were recruited from physical therapy clinics and orthopedic clinics in kaferelshiek city.

**The inclusion criteria** were patients aged 45 – 65 years old who had: (a) moderate or moderate to severe knee OA (grade II or III according to the radiological classification of knee OA defined by Kellgren and Lawrence.[20]

**The exclusion criteria** were patients who had: (a) severe OA (grade IV according to the Kellgren–Lawrence system of classification); (b) history of rheumatologic or inflammatory diseases; (c) received oral or systemic corticosteroids during the 2 weeks prior to treatment; (d) received an intra-articular injection of hyaluronic acid agents during the previous month; (e) poorly controlled diabetes mellitus with fasting blood sugar greater than 11.1 mmol/L; (f) history of anticoagulation therapy; (g) history of prior total knee replacement surgery.

**The radiological criteria** of knee joint OA severities used in this study were based on the Kellgren–Lawrence classification: grade 0: normal; grade I: small osteophytes without clinical importance; grade II: definite osteophytes but normal joint space; grade III: definite osteophytes with moderate narrowing of joint space; grade IV: definite osteophytes with severe narrowing of joint space (20).

### Research ethics

The study procedure was in accordance with the ethical standards of the responsible local committee on human experimentation of faculty of physical therapy, Kaferelshiek University.
Before participating in the project, the aims of the study were explained orally to all the patients and written informed consents were obtained from all study participants.

### Study design:

This study was randomized placebo-controlled, double-blind study. Patients were randomly assigned into 3 groups each containing 20 patients with bilateral knee OA. Group (A) received iontophoresis of 50 % dextrose for 40 min 5 days per week for three months, group (B) Each patient received three intra-articular injections of dextrose at 1-month intervals in weeks 0, 4, and 8. During the procedure, each patient was placed in a supine position with the knee flexed at 10–15°, and the intra-articular injection landmark was determined below the superolateral part of the patella.[21] The injection site was located by a lateral approach; in patients without sufficient space on the lateral side, a medial approach was performed. Under sterile conditions, a composition of 8 ml of 50% dextrose and 2 ml of 1% lidocaine was injected by an expert physiatrist using a 22 gauge needle. And group (C) received sham iontophoresis for 40 min, 5 days per week for three months.

Randomization was allocated using the numbered envelop method, 20 Subjects were chosen randomly for intra articular injection while other 40 subjects were divided randomly into group A and C, subjects were blinded about which group they were allocated.

### Outcome measures

Baseline demographic findings and Western Ontario and McMaster Universities arthritis index (WOMAC) values, knee ROM, and pain severity at rest (seated) and in activity (after walking 6 m)

using the visual analogue scale (VAS) were recorded. The patients were evaluated for these parameters before allocated in their groups then after 4, 8, and 24 weeks later.

Knee ROM in flexion was determined in prone position using an international standard $360^0$ electro goniometer. The validity and reliability of this measuring device has been demonstrated by other researchers.[22]

Pain was measured using a 10 cm VAS. Pain intensity is classified using a range from 0 to 10, in which 0 = no pain at all and 10 = the worst possible pain. Patients were asked to sign the place on the VAS scale that corresponded to their pain level.

The WOMAC questionnaire is used to evaluate a patient's functions when diagnosed with rheumatic diseases, especially knee OA. The WOMAC is a 24-item questionnaire with three subscales measuring pain (five items), stiffness (two items), and physical function (17 items). Answers to each of the 24 questions are scored on five-point Likert scales (none = 0, slight = 1, moderate = 2, severe = 3, extreme = 4), with total scores ranging from 0 to 96. So, the maximum possible scores for WOMAC, pain, stiffness, and function are 96 (most severe), 20, 8, and 68, respectively. Higher scores indicate greater disease severity.[23]
Achievement of minimal clinical difference with regard to similar studies was calculated as 20% for total WOMAC score and 50% for overall improvement in this score. Repeated measures analysis of variance (ANOVA) was used to evaluate the serial changes of different variables during the treatment period. All data were analyzed using the Statistical Package for Social Sciences, version 16.0; $p < 0.05$ was considered to be statistically significant.

## RESULTS

Data analysis was performed using (SPSS) for windows evaluation version 16.0, descriptive statistics, Data collected were analyzed statistically using:

- Descriptive statistics (mean and standard deviation)
- Inferential statistics using student T test.

Pearson correlation coefficient to determine the correlation between changes occurs

**Table 1:** Changes in range of motion, visual analogue scale and Total Western Ontario and McMaster Universities arthritis index of group (B) during the study periods (24 weeks), with consideration that one patient withdraw at the end of evaluation

| Evaluation intervals variable | At initial evaluation (Baseline) (0 week) | Before 2nd injection (4 weeks) | Before 3rd injection (8 weeks) | Final of evaluation (24 weeks) | *p* value |
|---|---|---|---|---|---|
| Number of knees | 40 | 40 | 40 | 38 | |
| Range of motion (˚) | 101.54 ± 10.34 | 107.34 ± 7.34 | 116.65 ± 6.23 | 121.67 ± 5.67 | *< 0.001 |
| Percentage$ changes | – | 10.7% | 27.9% | 37.27% | |
| Point changes‡ | – | 5.8 ± 3.01 | 15.11 ± 4.10 | 20.13 ± 4.67 | |
| Visual pain analogue scale | 8.98 ± 1.01 | 6.12 ± 1.05 | 5.08 ± 1.95 | 5.08 ± 1.05 | *< 0.001 |
| Percentage changes$ | – | 27.76% | 39% | 39% | |
| Point changes‡ | | -2.86 ± 0.04 | -3.96 ± 0.94 | -3.96 ± 0.04 | |
| Total Western Ontario and McMaster Universities arthritis index | 50.13 ± 12.32 | 30.15 ± 7.01 | 28 ± 6.01 | 26.65 ± 3.91 | *< 0.001 |
| Percentage$ changes | – | 39.96% | 44.26% | 46.96% | |
| Point changes‡ | – | -19.98 ± 5.31 | -22.13 ± 6.31 | -23.48 ± 8.41 | |

As shown in table 1 there were significant increase in range of motion (Percentage changes 32.72 %) from initial evaluation up to final evaluation (24 weeks), there were also significant decrease in Visual pain analogue scale by 39% Percentage changes and there were significant improve in Total Western Ontario and McMaster Universities arthritis index by 46.96% Percentage changes

*$p$ is two-sided significant (< 0.05) using repeated measures of analysis of variance statistical test.

$Improvement percentage of measured values is calculated by dividing the amount of changes at each level on the maximum of expected change (155 ± 5) and multiplying it by 100.

**Table 2:** Changes in range of motion, visual analogue scale and Total Western Ontario and McMaster Universities arthritis index of group (A) during the study periods (24 weeks).

| Evaluation intervals variable | At initial evaluation (Baseline) (0 week) | (4 weeks) | (8 weeks) | Final of evaluation (24 weeks) | *p* value |
|---|---|---|---|---|---|
| Number of knees | 40 | 40 | 40 | 40 | |
| Range of motion (˚) | 101.14 ± 8.14 | 112.30 ± 6.30 | 119.25 ± 2.23 | 129.67 ± 5.67 | *< 0.001 |
| Percentage$ changes | – | 20.66% | 33.53% | 52.83% | |
| Point changes‡ | – | 11.16 ± 3.01 | 18.11 ± 4.10 | 28.52 ± 4.67 | |
| Visual pain analogue scale | 8.38 ± 1.01 | 5.67 ± 1.15 | 4.89 ± 1.05 | 4.08 ± 1.75 | *< 0.001 |
| Percentage changes$ | – | 27.1% | 34.9% | 43% | |
| Point changes‡ | | -2.71 ± 0.04 | -3.49 ± 0.94 | -3.96 ± 0.04 | |
| Total Western Ontario and McMaster Universities arthritis index | 50.13 ± 12.32 | 28.15 ± 5.11 | 24.6 ± 3.71 | 23.05 ± 4.93 | *< 0.001 |
| Percentage$ changes | – | 43.96% | 52.26% | 54.16% | |
| Point changes‡ | – | -21.98 ± 5.31 | -25.53 ± 6.31 | -27.08 ± 8.41 | |

As shown in table 2 there were significant increase in range of motion (Percentage changes 52.83%) from initial evaluation up to final evaluation (24 weeks), there is also significant decrease in Visual pain analogue scale by 43% Percentage changes and there were significant improve in Total

Western Ontario and McMaster Universities arthritis index by 54.16% Percentage changes

*$p$ is two-sided significant (< 0.05) using repeated measures of analysis of variance statistical test.

§Improvement percentage of measured values is calculated by dividing the amount of changes at each level on the maximum of expected change (155 ± 5) and multiplying it by 100.

**Table 3:** Changes in range of motion, visual analogue scale and Total Western Ontario and McMaster Universities arthritis index of group (C) during the study periods (24 weeks)

As shown in table 3 there were no significant increase in range of motion (Percentage changes 8.09 %) from initial evaluation up to final evaluation (24 weeks), there were also no significant decrease in Visual pain analogue scale by 4.9% Percentage changes and there were no significant improve in Total Western Ontario and McMaster Universities arthritis index by 5.88% Percentage changes

| Evaluation intervals variable | At initial evaluation (Baseline) (0 week) | (4 weeks) | (8 weeks) | Final of evaluation (24 weeks) | *p value |
|---|---|---|---|---|---|
| Number of knees | 40 | 40 | 40 | 40 | |
| Range of motion (°) | 101.84 ± 9.12 | 104.33 ± 8.40 | 104.35 ± 8.23 | 105.97 ± 8.56 | * < 0.13 |
| Percentage§ changes | – | 4.88% | 4.92% | 8.09% | |
| Point changes‡ | – | 2.49 ± 0.28 | 2.51 ± 0.89 | 4.13 ± 0.56 | |
| Visual pain analogue scale | 8.38 ± 1.01 | 8.01 ± 2.13 | 7.88 ± 2.15 | 7.91 ± 1.55 | * < 0.72 |
| Percentage changes§ | – | 3.7% | 5% | 4.7% | |
| Point changes‡ | | -0.37 ± 0.04 | -0.5 ± 0.94 | -0.47 ± 0.04 | |
| Total Western Ontario and McMaster Universities arthritis index | 50.13 ± 4.12 | 51.12 ± 4.32 | 52.7 ± 2.01 | 53.07 ± 1.92 | * < 0.12 |
| Percentage§ changes | – | 1.98% | 5.14% | 5.88% | |
| Point changes‡ | – | .99 ± 0.20 | 2.57 ± 2.11 | 2.94 ± 2.2 | |

*$p$ is two-sided significant (< 0.05) using repeated measures of analysis of variance statistical test.§Improvement percentage of measured values is calculated by dividing the amount of changes at each level on the maximum of expected change (155 ± 5) and multiplying it by 100.

**Table 4:** Post hoc comparison of the tested parameters at post treatment

| | VAS | | ROM | | (WOMAC) | |
|---|---|---|---|---|---|---|
| | t | p | t | p | t | p |
| Placebo Vs iontophoresis | 7.7 | < 0.000* | 10.8 | < 0.000* | 11.9 | < 0.000* |
| Placebo Vs prolotherapy | 3.8 | < 0.006* | 3.7 | 0.01 | 8.9 | 0.001* |
| iontophoresis Vs prolotherapy | 8.6 | < 0.000* | 9.5 | < 0.000* | 10.4 | < 0.000* |

Represent the results of post hoc test for comparison between each two groups at post treatment and showed that, compared to sham group (placebo) there were significant improvement of VAS and ROM of iontophoresis group than sham (placebo) group($p < 0.000$). Also there were significant improvement of prolotherapy group than placebo ($p < 0.006$, and 0.02) respectively. Furthermore there was significant improve of iontophoresis group than prolotherapy where p was < 0.000 for VAS, ROM and (WOMAC).

## DISCUSSION

Osteoarthritis, commonly known as wear-and-tear arthritis, is a condition in which the natural cushioning between joints -- cartilage -- wears away. When this happens, the bones of the joints rub more closely against one another with less of the shock-absorbing benefits of cartilage. The rubbing results in pain, swelling, stiffness, decreased ability to move and, sometimes, the formation of bone spurs.[24]

The current study was conducted to investigate the effectiveness of dextrose iontophoresis versus dextrose prolotherapy in case of knee osteoarthritis in improvement of ROM, pain and functional ability of patients.

The results of current study demonstrated that both dextrose iontophoresis and dextrose phototherapy improved knee ROM and decrease pain, improve functional abilities as well as improve functional use of affected limbs, on an attempt to explain this effect, it could be attributed to influence of dextrose on ions motion across the cell membrane which may enhancing cell function and stimulates the proliferation of chondrocytes, osteocytes, and fibroblasts. These cells then excrete extracellular matrix, which enhances the stability of the joints by tightening and strengthening the ligaments, tendons, and joint stabilizing structures. [25-27]

Furthermore, the current study proposed that dextrose iontophoresis applied with currents up to 5mA produce better effects on ROM, pain reduction and functional abilities more than dextrose prolotherapy. To explain this effect we have to make scoping of effect of both methods on cells and microcirculation.

Prolotherapy has been reported as a useful method in the treatment of chronic musculoskeletal and joint diseases. It is proposed that prolotherapy causes mild inflammation and cell stress in the weakened ligament or tendon area, releases cytokines and growth factors, and induces a new healing cascade in that area, which leads to activation of fibroblasts, generation of collagen precursors, and strengthening of the connective tissue.[28]

The rationale for prolotherapy is that it may produce dense fibrous tissue to strengthen the attachment of ligaments, tendons, joint capsules, and other fascial structures at their fibro-osseous junctions.[29]
In a study by Hooper et al., intra-articular zygapophysial joint prolotherapy using 0.5–1mL of dextrose solution improved pain and function in patients with chronic whiplash which agree with results of our study.[30]

Our results agree with Reeves et al. who reported that intra-articular dextrose prolotherapy resulted in clinically and statistically significant improvements in knee osteoarthritis, with or without anterior cruciate ligament laxity.[31, 32]

In spite of the clinical effectiveness of dextrose prolotherapy, we encourage caution in its use because it is indiscriminate in breaking down the intercellular ground substance matrix. In so doing, it may open a path for infection or other toxins, and may damage articular cartilage. Also it was reported that many patients withdraw from prolotherapy because of severe pain and soreness occurred after injection.[33]

In other hand in dextrose iontophoresis, it is assumed that the effects of the treatment are attributed to the delivered ions and not the direct current.[34]

The ions are driven into the skin via the pores - hair follicles, sweat gland ducts - rather than through the stratum corneum (the stratum has a high resistance, thus limited current passes through it - the ducts are lower resistance, will allow greater passage of current, thus the route of preference).[35]

Moreover, articular chondrocytes have special transporter systems for glucose and ascorbic acid.[36] Glucose is delivered to the chondrocytes via synovial microcirculation and taken up by glucose uptake (GLUT) proteins. The intracellular glucose pool is used for glycolysis and extracellular matrix macromolecules.[37] The supply of glucose for anaerobic metabolism is essential to the survival and proliferation of chondrocytes and for the maintenance of matrix integrity. Therefore, impaired glucose uptake would compromise chondrocyte function, and potentially result in an imbalance in cartilage matrix synthesis and degradation, leading to OA.[38] Which may explain the role of dextrose in maintaining articular cartilage matrix integrity.

The evidence is summarized by Belanger (2010) who concludes that based on the available evidence[39], (e.g. kalia et al, 2004) the penetration of the ions is greatest in the region of the pores, the penetration of the substance through the skin is in proportion to the current magnitude, but that the substance is most likely deposited below the stratum corneum, thus acting as a depot. Onward migration of the substance to the deeper tissues is achieved by diffusion rather than being 'driven' deeper by the applied current.[40]

Russo et al disagree with our results who reported that lidocaine applied by iontophoresis was more effective for producing skin anesthesia than when it is applied by swabbing, however, was not as effective as injection. Although these investigators examined skin anesthesia for injection or minor surgical procedures, they demonstrated that lidocaine had a deeper, longer-lasting effect when applied by iontophoresis than when it was swabbed on. The method of application could be a consideration when cutaneous anesthesia is used in physical therapy to modulate kinesthesia from skin or superficial joint receptors.[41]

One of the most hazards of iontophoresis is skin burn which may consider a risk for patient but we overcome that problem by using Constant current which is preferable than constant voltage - thus, whatever changes occur in terms of skin resistance, the magnitude of the applied current will not exceed the preset level. And if that is the case, constant current will give you an effective and the safest application (smaller risk of skin burn).

Regarding the improvement of the WOMAC questionnaire, pain reduction and increase knee ROM of both dextrose iontophoresis and dextrose prolotherapy but up to our knowledge and review of literature, no study comparing and investigating the effect of dextrose iontophoresis versus dextrose prolotherapy which were reported to be effective in treatment of osteoarthritis.

The present study demonstrate higher percent of improvement of symptoms and function as presented in WOMACQ of group A (54.16%) than percent of improvement of group B (46.96) also in goniometric measurement there was obvious increase in ROM after treatment in group A (52.83%) which more than obtained in group B (37.27%), also in visual analogue scale for pain there is higher percent of improvement of group A (43%) than in group B (39%)

The explanation might be beside direct effects of dextrose, iontophoresis consider noninvasive method of delivering dextrose into knee in safer manner and less painful which may be due to

1. Avoids the risks and inconveniences of parenteral (injection/intraarticular)therapy

2. Increases therapeutic efficacy by bypassing hepatic "first-pass" elimination-the reduction in the amount of the drug entering the systemic circulation, due to metabolism by the liver as the drug passes through the hepatic circulation after absorption from the gastrointestinal tract
3. Reduces the chance of overdosing or under dosing by providing continuous delivery of the drug, programmed at the required therapeutic rate
4. Permits the use of a drug with a short biological half-life because (1) the drug is delivered directly to the target organ without the need to circulate and recirculate in the blood or (2) the drug is delivered directly into the bloodstream without delays due to absorption through the gastrointestinal tract
5. Provides a simplified therapeutic regimen, leading to better patient compliance
6. Permits a rapid termination of administration of the medication, if needed, by simply turning off the iontophoresis delivery system.

Weakness of this study include a relatively small sample size, though the effect size of dextrose prolotherapy and iontophoresis proved adequate to detect between-group differences. The study was not large enough to detect uncommon adverse events, such as intolerance to study medication or rare injection-related squeal and also follow up for a short period of time (24 weeks). Generalizability may be limited by numerous exclusion criteria, the relative youth of the cohort compared with those in some knee osteoarthritis studies, and the relative lack of participants with very severe baseline WOMAC scores.

The assessment of participant satisfaction was indirect and subject to bias. Radiographs were not available for all participants, and the use of Kellgren-Lawrence criteria for baseline radiological assessment of knee osteoarthritis severity is controversial. The Kellgren-Lawrence score, however, is likely to remain an important measure for gauging disease severity in symptomatic patients.[42]

## CONCLUSION

The results of this study indicated that both dextrose iontophoresis and dextrose prolotherapy may be as useful modalities in treatment of osteoarthritis with better effects of dextrose iontophoresis than prolotherapy However, this study also has some limitations. There was a need for more frequent intervention by intra articular Prolotherapy Further investigations are necessary to evaluate the long term safety of repeated intra-articular injection of dextrose water and the adequacy of the volume and number of injections as well as Further studies are needed to validate an appropriate iontophoresis protocol., although no patient here reported a serious adverse event.

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