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Meta-Analysis

Hypertonic dextrose compare with other substances for knee osteoarthritis: a meta-analysis of randomized control trial

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ABSTRACT

Background: Globally, osteoarthritis (OA) highly prevalent in the elderly more than 80% of those over 55 years old. At least 151 million people worldwide are afflicted. The knees, hips and spine are the joint areas that are most frequently affected. For the treatment of knee OA, intra-articular injection like stem cells, platelet rich plasma (PRP), and hypertonic dextrose (HD) the most used prolotherapy fluid is HD. It is widely accessible, reasonably inexpensive priced and reportedly safe. The aim of this meta-analysis is to thoroughly assess and compare the results of intra articular dextrose prolotherapy with hyaluronic acid and normal saline, with a focus on visual analog scale (VAS) and WOMAC score.
Methods: A comprehensive search was conducted across major electronic databases for relevant studies published from 2014 to 2024. Studies that compare intra articular dextrose prolotherapy with hyaluronic acid and normal saline for knee OA were included. We recorded the first author, year, study design, sample number, age, sex, Kellgren Lawrence grade, VAS and WOMAC score were extracted and analyzed using appropriate statistical methods.
Results: The initial search yielded a total of 2371 studies, of which 7 studies met the inclusion criteria, consisting of a total of 372 patients of intra articular dextrose prolotherapy with hyaluronic acid and normal saline for knee OA. It shows that there is no significant difference in VAS score between two groups (MD=-0.72, 95% CI:-1.74 to 0.31, p=0.17). There was no difference in WOMAC score between two groups.
Conclusions: Our results show that both methods provide similar outcome in pain scale and WOMAC score. More over to enhance the efficacy of prolotherapy in comparison to alternative treatments like HA or saline injections, it is suggested that a multicenter clinical trial with a larger number of participants be carried out.

Keywords: Knee OA, Dextrose prolotherapy, Hyaluronic acid, Normal saline

INTRODUCTION

Globally, OA is the most common type disease of joint. It is highly prevalent in the elderly and closely correlated with age; according to some studies, more than 80% of those over 55 years old have OA in at least one joint. At least 151.4 million people worldwide are afflicted with this illness.[1,2] The knees, hips, hands, feet, and spine are the joint areas that are most frequently affected. The reason hip and knee OA are the most significant is that they are the most common causes of pain and impairment in the elderly and because they need a significant amount of healthcare resources, especially when it comes to joint replacements. Focal areas inside joints are impacted by OA; initially, the diseases only affect a small area, but it may eventually spread to the entire joint. Growing older is a significant risk factor, with variations in its distribution and prevalence in men and women. The variability of OA is attributed to a varied combination of many risk factors that influence various individuals and different joint sites, rather than a single cause. Systemic cause as a result of: Age, gender, genetics, obesity, and

diet. The following are local factors: abnormal joint size and form; prior injuries; neuromuscular issues; obesity; loading/occupational concerns. To evaluate the degree of radiographic changes, several scoring methods are available. The Kellgren and Lawrence scoring method, which classifies OA X-ray changes into five categories, is the most widely used: 0 normal, 1 Doubtful Minimal osteophyte, doubtful significance, 2 minor definite osteophyte, no loss of joint space, 3 Moderate Some diminution of joint space and 4 severe advanced joint space loss and sclerosis of bone.[1] The most common sites for knee OA is the medial tibiofemoral joint, although it can affect any of the three compartments and is frequently tricompartmental. Upon examination, there is a perceptible and occasionally audible crepitus during movement, antalgic gait, quadriceps muscle atrophy, joint effusion, and joint deformity. Passively correcting the joint deformity might be possible.[3]

There are numerous guidelines and a wide range of therapies available for the treatment of individuals with OA. In order to relieve pain and restore function, the current treatments mostly focus on symptom remission. For the treatment of knee OA, intra-articular injection has been shown to be a safe and successful minimally invasive approach.[4] Prolotherapy was initially utilized in the 1950s to treat ligamentous laxity and musculoskeletal disorders because the initial effect of promotes healing and fibrosis. Prolotherapy is a nonsurgical regenerative injection procedure that stimulates the growth of normal cells and tissues by introducing small volumes of an irritating solution to the location of sore or deteriorated tendon insertions, joints, ligaments, and adjacent joint spaces. The most often utilized irritating solutions are stem cells, PRP, and HD.[5]

The most used prolotherapy fluid is HD. It is widely accessible, reasonably inexpensive priced, and reportedly safe. The most popular prolotherapy solution is HD (with doses ranging from 12.5 to 25%), which has been proved in numerous clinical trials to provide positive results.[6] Because HD is water soluble, a normal component of blood chemistry, and it can be injected safely into different places in huge quantities, it is thought to be a suitable substances. For many years, HD infiltration over ligament and tendon insertions has been applied intra- or extra-articularly to treat musculoskeletal discomfort. When it comes to treating knee OA, hypertonic dextrose prolotherapy (HDP) is still not very effective due to a lack of reliable scientific evidence.[7,8]

Thus, in order to examine the therapeutic usage of HD vs. another class of drugs in patients with knee OA, we carried out this meta-analysis. to evaluate each substance's effectiveness, qualities in use, and to make clear any nuances in benefits, drawbacks, or therapeutic considerations. We hypothesized that in patients with symptomatic knee OA, HDP may reduce pain and enhance knee function.

METHODS

Search strategy and study selection

This meta-analysis conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The search was performed in September 2024 (focusing on 2014-2024 RCT research) on Pubmed, Cochrane library and Science Direct. The search strategy used keywords conforming to medical subject headings (MeSH) to identify relevant articles. The search terms used were "(hypertonic dextrose OR dextrose injections OR dextrose prolotherapy) AND (normal saline) AND (hyaluronic acid) AND "(knee osteoarthritis OR osteoarthritis of knee)" The present study was conducted according to the PRISMA.[9] Preliminary guideline protocol was compiled: P (patient): knee osteoarthritis; I (intervention): dextrose solution; C (comparison): hyaluronic acid or normal saline solution; O (outcomes): VAS and WOMAC score.

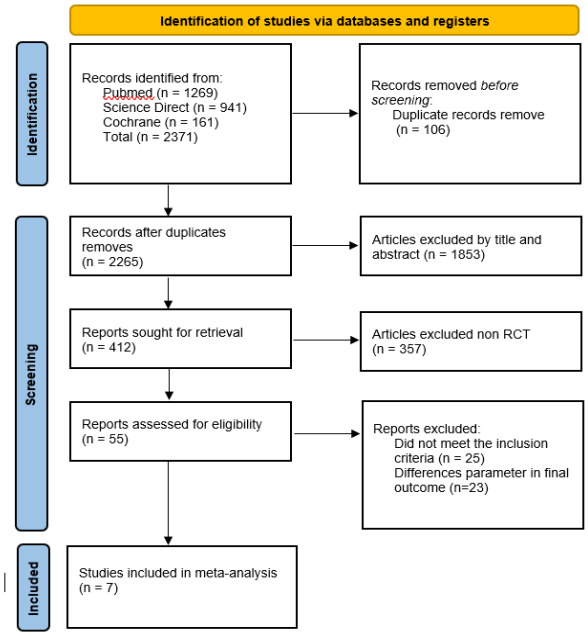

Figure 1: Prisma flow chart of literature search.

Inclusion and exclusion criteria

The following inclusion criteria had to be met: randomized control trial research, patients with confirmed knee OA case, treated with dextrose solution and compared with normal saline or hyaluronic acid, data published in English and full text. Studies not in English, other subtances treatment, and all study except RCT were excluded.

Methodological quality assessment

For the methodological quality assessment, the review manager software version 5.4 was used. Two authors independently performed the assessment. The Cochrane

risk of bias assessment (RoB) tool analyses the included articles with regard to five aspects: selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, and reporting bias, shown in Figure 2.

Data extraction and analysis

Author examined all the identified studies and extracted data using a predetermined form. We recorded the first author, year, study design, enrolled sample number, age, sex, Kellgren-Lawrence grade, VAS and the WOMAC score. The WOMAC is the most widely used disease-specific instrument for the assessment of treatment effects in patients with OA. This instrument consists of 24 items and 3 subscales. The pain, stiffness, and physical function subscales were reported as adequate in content and construct validity, as well as responsiveness, in patients with knee OA.[13] Statistical analysis was conducted using review manager version 5.4.1, employing a random-effects model to assess heterogeneity between studies. Forest plots were used to visualize outcomes, and significance was determined at $p<0.05$.

RESULTS

A total of 2371 articles from 3 database were initially identified. Total 106 study removed after duplication, 1853 excluded by title and abstract, 357 excluded because non-RCT study, 28 excluded because did not meet the inclusion criteria and reported differences outcome parameter. Subsequently, after underwent assessment, 7 studies met the eligibility criteria with a total of 372 patients.[10-16] Prisma flow chart shown in Figure 1 and risk of bias assessment is shown in Figure 2. The demographic characteristics are outlined in Table 1, treatment detail and follow up duration in Table 2.

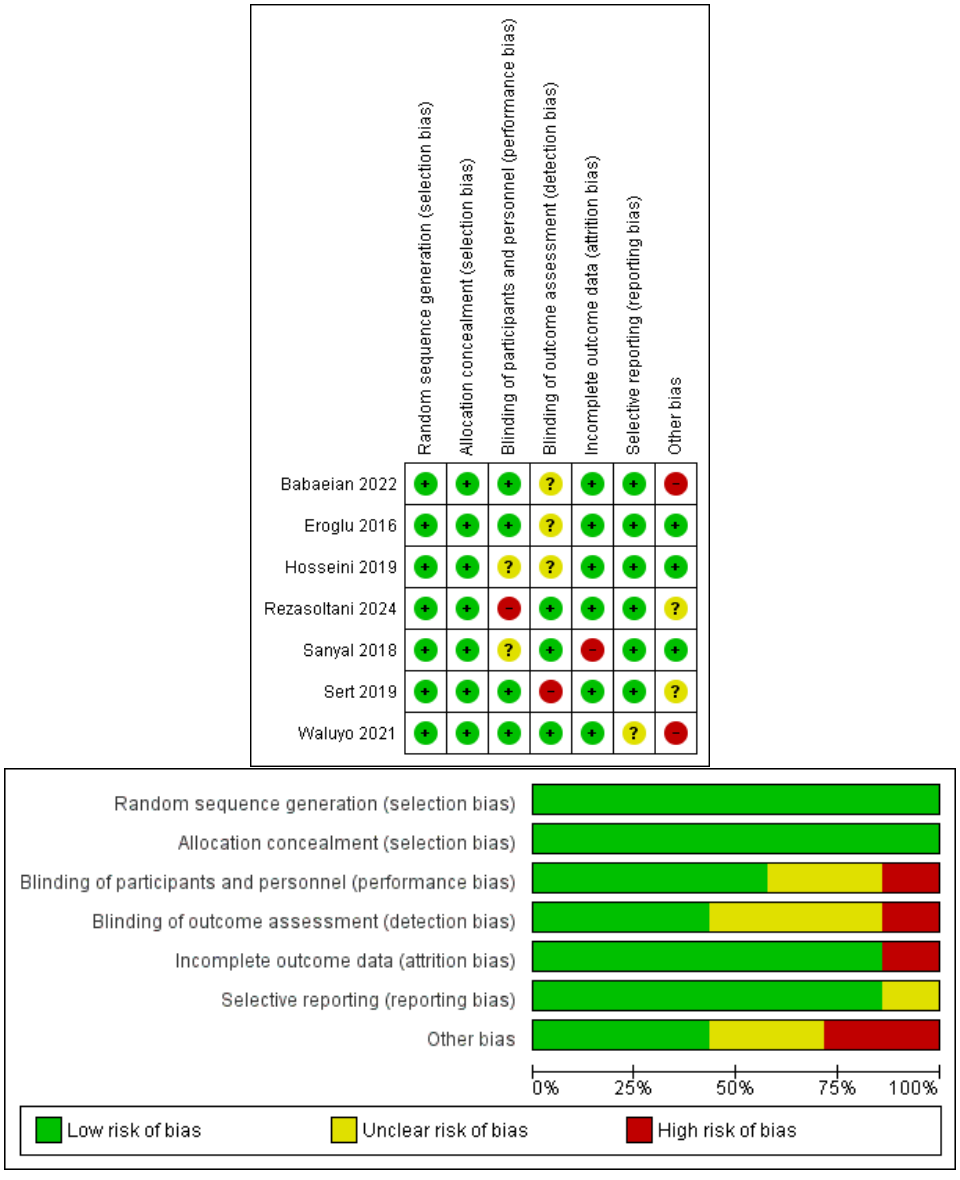

Figure 2: Risk of bias graph and summary of the included studies.

Table 1: The characteristics of included studies.

Study	Year	Country	Patients		Age (in years)		Kellgren-Lawrence grade	Total patients/ male
			Dextrose	HA or NS	Dextrose	HA or NS		
Eroglu[10]	2016	Turkey	20	20	66.00±5.79	62.00±6.46	I-III	40/2
Sanyal[11]	2018	India	15	15	58.27±1.6	58.20±1.3	I-III	30/10
Hosseini[12]	2019	Iran	52	52	61.2±11.5	63.7±12.2	II-IV	104/62
Sert[13]	2019	Turkey	21	22	55.7 ± 6.6	54.4±7.3	II-III	43/5
Waluyo[14]	2021	Indonesia	26	21	62.6 (6.9)	62.0 (10.8)	I-IV	47/12
Babaeian[15]	2022	Iran	24	21	60.16±9.07	57.45±10	II-III	45/8
Rezasoltani[16]	2024	Iran	33	30	63.9±9.11	66.0±10.24	III-IV	63/6

Table 2: Treatment detail and follow up duration of included studies.

Study	Treatment Detail		Follow up duration
	Dextrose	HA or NS	
Eroglu[10]	dextrose prolotherapy 3 times with 3 weeks interval, 6-mL intra-articular injection then delivered using an inferomedial approach.	0,09% NaCl 3 times with 3 weeks interval with same injection amounts and method as in prolotherapy group	3 and 6 months
Sanyal[11]	25% dextrose and 2% preservative free Lignocaine were mixed in a syringe to give a final concentration of dextrose 12.5% with 1% lignocaine. Four ml of the mixture was injected into the joint	injected with 4 ml of hyaluronic acid intra articularly after proper antisepsis.	2 months
Hosseini[12]	10 mL of 12.5% HD through 4 point injection	2.5 mL of hyaluronic acid injected intra-articulary via inferomedial of patella.	3 months
Sert[13]	5 mL injection of 25% dextrose solution (4 mL 30% dextrose +1 mL 0.9% sodium chloride)	intra-articular (2.5 mL 0.9% sodium chloride +2.5 mL 1% lidocaine) and extra-articular (5 mL 0.9% sodium chloride +5 mL 1% lidocaine)	6 and 18 weeks
Waluyo[14]	5 ml 25% intra-articular dextrose injection and 30-40 ml 15% peri-articular dextrose injection	2 ml Adant® (hyaluroan) intra-articular injection (~10 mg)	3 months
Babaeian[15]	3 ml of dextrose with 50% concentration was diluted with 3 ml of lidocaine 2%	3 ml of saline with 5% concentration was diluted with 3 ml of lidocaine 2%	4 weeks
Rezasoltani[16]	injections of 9 mL of 20% dextrose plus 1 mL of lidocaine 2%	Intra-articular inj of 5 cc of 5% hypertonic saline solution (the most common injectable type of hypertonic saline in Iran) plus 1 ml of lidocaine 2%	6 months

VAS

Six studies reported data on VAS after interventions between HD versus hyaluronic acid or normal saline for knee OA including 332 total patients. Heterogeneity exists between the six studies (Chi^2=45.79, df=5, p<0.00001, I^2=89%) using a random-effects model It shows that there is no significant difference (MD=-0.72, 95% CI:-1.74 to 0.31, p=0.17), (Figure 3).[11-16]

WOMAC total score

Four studies reported data on WOMAC total score after interventions between HD vs hyaluronic acid or normal saline for knee OA including 160 total patients.[10-14] Heterogeneity exists between the six studies (Chi^2=17.03, df=3, p=0.0007, I^2=82%) using a random-effects model It shows that there is no significant difference (MD=-6.20, 95% CI: -13.26 to 0.86, p=0.09), (Figure 4).

WOMAC pain score

Three studies reported data on WOMAC pain score after interventions between HD versus hyaluronic acid or normal saline for knee OA including 129 total patients. Heterogeneity exists between the six studies (Chi^2=5.14, df=2, p=0.08, I^2=61%) using a random-effects model It shows that there is no significant difference (MD=-1.54, 95% CI: -3.32 to 0.23, p=0.09), (Figure 5).[10-14]

WOMAC stiffness score

Three studies reported data on WOMAC stiffness score after interventions between HD versus hyaluronic acid or normal saline for knee OA including 129 total patients. Heterogeneity exists between the six studies (Chi^2=9.06, df=2, p=0.01, I^2=78%) using a random-effects model It shows that there is no significant difference (MD=-0.14, 95% CI: -1.25 to 0.97, p=0.81), (Figure 6).[10-14]

WOMAC functional score

Three studies reported data on WOMAC functional score after interventions between HD versus hyaluronic acid or normal saline for knee OA including one hundred and twenty nine total patients. Heterogeneity exists between the six studies (Chi^2=11.14, df=2, p=0.004, I^2=82%) using a random-effects model It shows that there is no significant difference (MD=-2.66, 95% CI: -10.67 to 5.35, p=0.51), (Figure 7).[10-14]

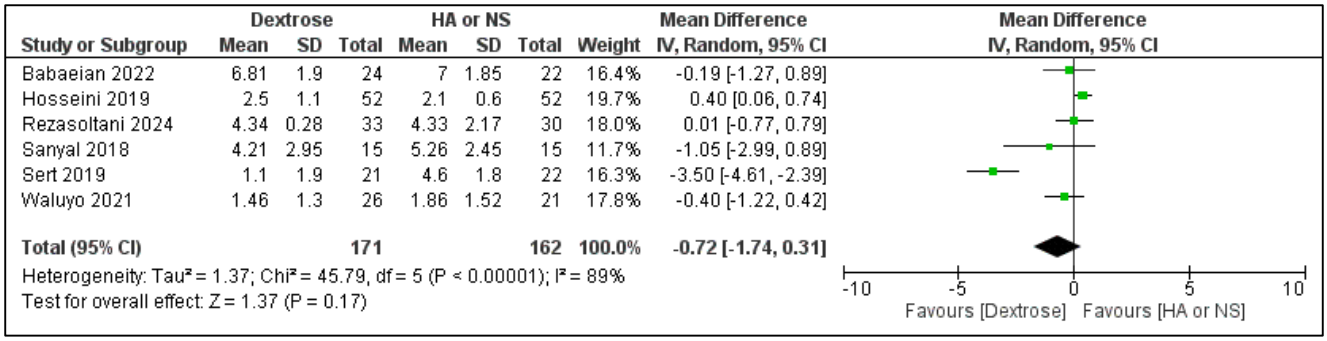

Figure 3: Analysis of VAS between two groups.

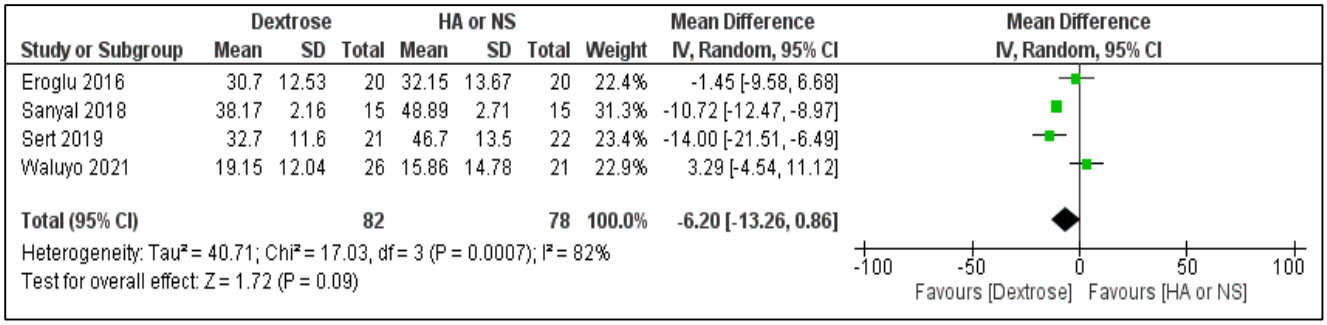

Figure 4: Analysis of WOMAC total score between two groups.

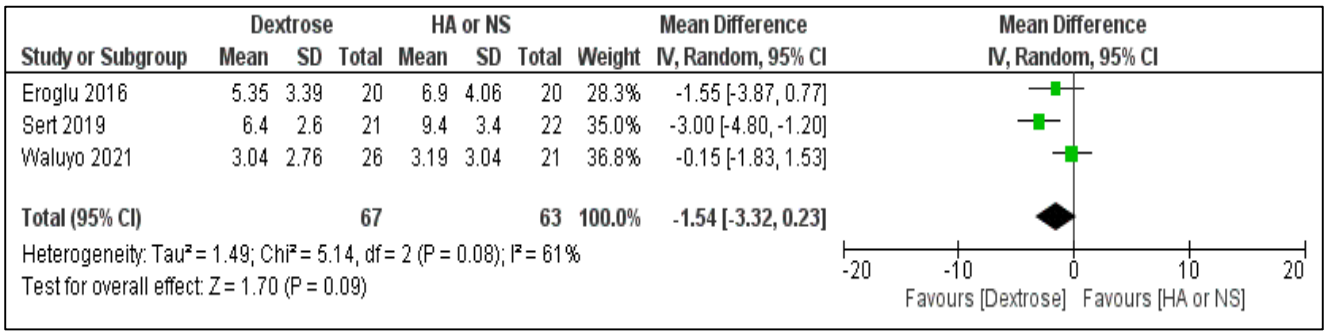

Figure 5: Analysis of WOMAC pain score between two groups.

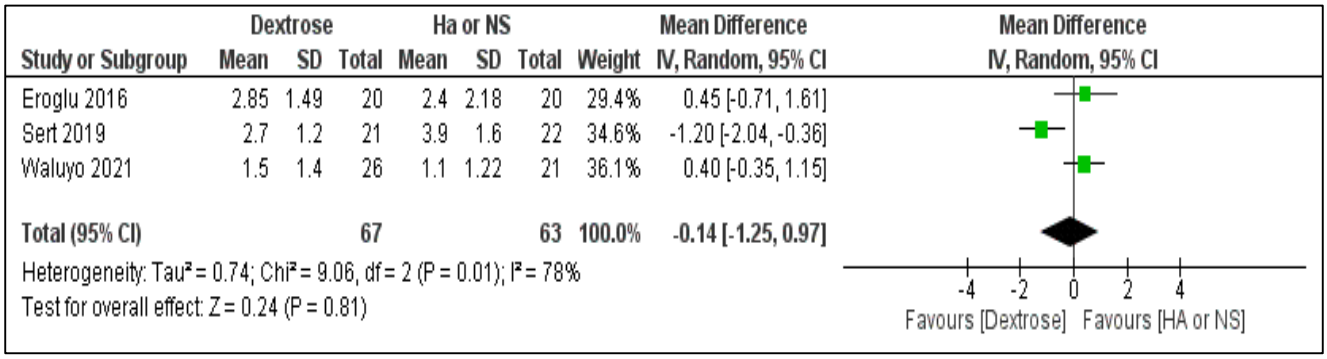

Figure 6: Analysis of WOMAC stiffness score between two groups.

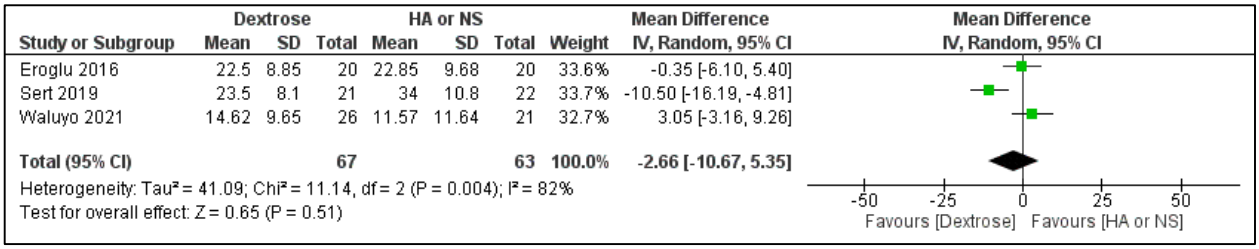

Figure 7: Analysis of WOMAC functional score between two groups.

DISCUSSION

The dextrose method involves reducing local inflammation. In knee OA patients, this may be achieved by injecting a proliferative solution, which also helps to promote healing and reduce inflammation. This could potentially ease pain and stiffness. Another proposed mechanism is the stimulation of proliferation in soft tissues or joints, whereby prolotherapy solutions such as dextrose promote tissue development and repair, ultimately resulting in enhanced joint function. Prolotherapy has also been associated with decreased pain by modifying pain signals and delivering analgesic effects by injecting the affected area.[17] In order to treat knee OA, prolotherapy involves injecting a solution-typically containing ingredients like dextrose and lidocaine near the painful or injured joints to trigger an inflammatory reaction. When given, dextrose a form of sugar can in fact cause inflammation, especially when taken quickly. Dextrose solutions have the ability to cause an inflammatory response in prolotherapy, which sets off the body's natural healing mechanisms. Tissues like tendons, ligaments, and cartilage require this inflammatory response to heal and regenerate.[18] In prolotherapy, the inflammatory reaction sparked by dextrose is an essential component of the healing process because it encourages the synthesis of growth factors required for tissue development and repair. Consequently, in the context of prolotherapy, dextrose is helpful in promoting tissue healing and regeneration even if it may initially cause inflammation. Fibroblasts, the body's repair cells, are produced in large quantities during this phase, which results in the deposition of new tissue fibers that heal the lesion, stabilize the area, return function, and lessen discomfort. Prolotherapy is thought to initiate an inflammatory cascade that encourages tissue remodeling and proliferation, hence facilitating the healing process People with knee OA may experience less pain and more comfort as a result of this. In the end, prolotherapy patients report better pain, function, and overall quality of life, which adds to their overall happiness with the treatment. Although more research is need to determine the exact processes underlying these improvements, prolotherapy has demonstrated promise as a therapeutic alternative for knee OA patients.[19,20]

The primary constituent of articular fluid, HA, gives joints their viscoelastic and lubricating properties.[21] It plays a role in anti-inflammatory, proteoglycan, glycosaminoglycan, and chondroprotection production. Furthermore, intra-articular HA injections can dramatically lower chondrocyte apoptosis rates.[22] Clinical studies have demonstrated that HA injections can potentially lessen knee discomfort, enhance function, and enhance quality of life in knee OA patients.[23] The typical mechanism of action of saline is the diluting of inflammatory mediators in the knee, which relieves subjective stiffness and pain perception. As previously mentioned, the effectiveness of the intricate interaction of psychological elements underlying the "placebo effect" cannot be disregarded as a potential avenue for this improvement. Whatever the reason, such dramatic gains in function and discomfort indicate that intra articular normal saline should be further investigated as a possible knee OA treatment. Finding a suitable control for intra articular normal saline would still be difficult, though. Some worries about the possible biological therapeutic impact of intra articular normal saline would presumably be allayed with a sham group that received a simple needle stick into the joint.[24]

Wee and colleagues did a meta-analysis in 2021.[25] An update on current understanding of the application of dextrose prolotherapy in knee OA is given by this systematic review. Overall, it seems that patients with knee OA can benefit from dextrose prolotherapy in terms of pain relief and improved function. A study by Khateri et al detailed the examination and evaluation of a number of tools, including WOMAC, VAS, and KOOS.[26] This study's investigation of the length of prolotherapy follow-up and the intervention's long-term impact in knee OA patients is another benefit. This meta-analysis indicates that prolotherapy can alleviate pain and stiffness for a maximum of twenty weeks. It is evident that the use of dextrose prolotherapy shows promise in lowering joint stiffness and discomfort while also enhancing functional performance in knee OA patients. Comparing the HDP therapy group to the control group, Wang et al observed substantial improvements in knee function (SMD=1.30, 95% CI: 0.45-2.14; p<0.001; I2=91%), pain (SMD=1.33, 95% CI: 0.49-2.17; p<0.001; I2=91%), and overall WOMAC score (WMD=13.77, 95% CI: 6.75-20.78; p<0.001; I2=90%).[27] Given that all of the included studies did not reveal any significant side events associated with dextrose injection, HDP is a viable treatment for knee OA with a reasonable safety profile. Arias-Vázquez et al study prolotherapy using HD was superior to local anesthetic infiltrations in terms of

improving pain and function.[28] It was also comparable to infiltrations using hyaluronic acid, ozone, or radiofrequency, but less effective than PRP and erythropoietin. These results were positive in the short, medium, and long terms. Furthermore, no significant adverse responses or side effects were identified in individuals receiving HD.

Some limitations in the current study should be interpreted. First off, the primary drawback is that the majority of over analyses have a significant degree of heterogeneity. The conclusion's persuasiveness has been undermined by the substantial heterogeneity among the pooled results. Despite our efforts to make up for methodological flaws by using stratified analyses, several results remained ambiguous because the important elements were not documented in numerous papers. Second, the final result is biased due to the different follow-up durations found in the included studies. Thirdly, despite the fact that our data suggested a distinction between short-term and functional outcomes, our data only reported short-term results. Thus, more focused and published long-term follow-up surveys are required, and multicentered, large population-based designs should be considered in future research.

CONCLUSION

This study including the most recent evidence shows that in a selected group of patients suffering knee OA, dextrose and hyaluronic acid or normal saline are effective substances for knee OA cases. Our results show that both methods provide similar outcome in pain scale and WOMAC score. More over to enhance the efficacy of prolotherapy in comparison to alternative treatments like HA or saline injections, it is suggested that a multicenter clinical trial with a larger number of participants be carried out. Furthermore, future research should consider including postintervention follow-up periods to help make better decisions about how long the effects of prolotherapy last.

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