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Prolotherapy for knee osteoarthritis using hypertonic dextrose vs other interventional treatments: systematic review of clinical trials

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Abstract

Background: To evaluate the efficacy and safety of prolotherapy with hypertonic dextrose in patients with knee osteoarthritis. A systematic search was performed in electronic databases including PUBMED, SCIELO, DIALNET and Google Scholar.

Main body: We searched for randomized clinical trials that evaluated therapeutic interventions in patients with knee osteoarthritis. These trials compared the effect of intra-articular and / or extra-articular infiltrations of hypertonic dextrose vs the effect of intra-articular and / or extra-articular infiltrations of other substances or some interventional procedure application, via assessing pain, physical function and secondary effects and / or adverse reactions. Ten randomized clinical trials were included in this systematic review, the total sample size comprised 328 patients treated with hypertonic dextrose (prolotherapy) vs 348 controls treated with other infiltrations such as local anesthetics, hyaluronic acid, ozone, platelet-rich plasma or interventional procedures like radiofrequency.

Conclusions: In terms of pain reduction and function improvement, prolotherapy with hypertonic dextrose was more effective than infiltrations with local anesthetics, as effective as infiltrations with hyaluronic acid, ozone or radiofrequency and less effective than PRP and erythropoietin, with beneficial effect in the short, medium and long term. In addition, no side effects or serious adverse reactions were reported in patients treated with hypertonic dextrose. Although HDP seems to be a promising interventional treatment for knee OA, more studies with better methodological quality and low risk of bias are needed to confirm the efficacy and safety of this intervention.

Keywords: Prolotherapy, Hypertonic dextrose, Knee, Osteoarthritis

Introduction

The knee joint represents one of the anatomical locations that most frequently suffer osteoarthritis (OA) [1], which increases with age and has a prevalence of 15.6% in men and 30.7% in women over 55 years old [2]. Osteoarthritis is a rheumatic disease that causes serious physical disability [3] and leads to high living costs [4].

There are several options for treating knee OA including non-pharmacological therapy, [5, 6] pharmacological treatment [5, 6] and interventional measures such as intra-articular infiltrations with corticosteroids [5, 6] or hyaluronic acid (HA) [6]. In recent years, new treatments have been reported to be effective for treating patients with knee OA, including intra-articular platelet-rich plasma application, [7, 8] mesenchymal stem cells, [9] ozone therapy, [10] hypertonic dextrose [11] and even the botulinum toxin type A [8].

Intra-articular or extra-articular applications of hypertonic dextrose infiltration over ligament and tendon insertions have been used for decades to treat musculoskeletal pain under the name of *Prolotherapy*; infiltrations are performed using hypertonic dextrose usually mixed with

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local anesthetics [12]. Nevertheless, Hypertonic Dextrose Prolotherapy (HDP) remains of little use when treating knee OA; given the lack of solid scientific evidence to support its benefits, it has been classified as a complementary therapeutic intervention. Therefore, the objective of our study was to conduct a systematic search of randomized clinical trials that compared the therapeutic use of HDP vs another type of placebo or therapeutic interventionist procedure in patients with knee OA, in order to analyze its efficacy, characteristics in its application, dosage and side effects or adverse reactions.

Methods

The methodology we used was based on the PRISMA statement [13] for systematic review and meta-analysis type reports presentation.

Types of studies

This review included Randomized Controlled Clinical Trials that used a therapeutic intervention with HDP vs other substances infiltration or some other performance interventional procedure for treating patients with knee OA. We excluded reviews, series of cases studies, reports of one case, randomized clinical trials performed in patients with knee OA that compared non-interventional treatments and studies performed for knee pathologies other than OA.

Characteristics of the participants

We selected studies that included individuals with clinical and radiographic diagnosis of knee OA, who suffer pain and alterations in functionality. All participants were adults of at least 18 years of age.

Types of intervention

We selected studies in which patients were treated with one or more HDP sessions in at least one of the groups studied; the intra-articular hypertonic dextrose infiltration sessions could be with or without complementary extra-articular infiltrations and /or concomitant local anesthetics.

Control groups consisted of individuals with knee OA treated with placebo or other therapeutic substances infiltrations or some other interventional procedure. Other co-interventions were allowed as long as they were uniform in all groups. The studies chosen had to describe in detail the intervention(s) performed, evaluations used and results.

Outcomes measures

We included studies that evaluated self-reported pain and / or self-reported physical function. Pain was assessed using the Visual Analogue Scale (VAS) [14], while function was assessed using other validated scales [15]. We categorized the results according with the follow-up time reported in each study, by grouping them into three categories: 2–3 months, 5–6 months and 12 months of follow-up.

Method and search strategy

We identified possible studies by searching in electronic databases PUBMED DIALNET, SCIELO databases and other electronic sources such as Google Scholar, using a search period from January 2000 to May 2018. The search terminology included prolotherapy “or” dextrose prolotherapy “or” hypertonic dextrose injections “and” knee “or” knee arthrosis “or” knee osteoarthritis.

Methodological quality and risk of bias assessments

Based on the Cochrane Handbook for Systematic Reviews recommendations, version 5.1 [16] two investigators independently assessed the methodological quality and risk of bias of each study included. The following domains were evaluated: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of participants and staff (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (report bias) and other biases. The risk of bias for each domain was classified as low, high, or uncertain. A trial was considered to have low bias risk only when all domains were rated as low. If 1 or 2 domains were classified as high or uncertain risk of bias, the trial was considered to have a moderate bias risk; if 3 or more domains were classified as high or uncertain risk of bias, then it was considered a trial with high bias risk. The evaluation summary of the risk of bias is shown in Fig. 1.

Eligibility assessment and data extraction

Two reviewers independently examined titles, abstracts and full texts, and determined the eligibility of each study. Data of eligible studies were extracted independently: study design, risk of bias, clinical configuration, participant characteristics, intervention features, outcomes, follow-up duration and adverse events.

Results

A total of 163 citations were identified; of those, 89 were duplicates and were excluded. We reviewed titles and abstracts of the remaining 74 studies and excluded 26 studies that were animal model revisions, editorials and others. Forty-eight studies were read in detail, then 38 were excluded for the following reasons: review studies ($n = 20$), other pathology interventions ($n = 9$), case series studies ($n = 7$), controlled clinical trials compared against non-interventional treatments ($n = 2$). Finally, 10 randomized clinical trials [17–26] were eligible for inclusion in this systematic review. The systematized flowchart search is shown in Fig. 2. The 10 studies comprised a total of 328 patients with knee OA treated with HDP and 348 controls treated with other interventional procedures. All studies included patients with knee OA of various degrees according to the Kellgren and Lawrence Classification (KL).

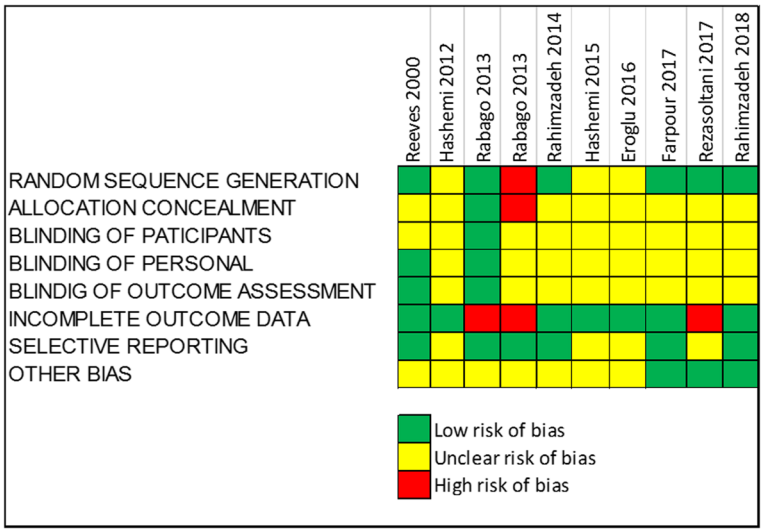

Fig. 1 Summary assessment about risk of bias

The design characteristics, intervention and results of each study are reported in Table 1.

Hypertonic dextrose vs saline solution - lidocaine mixture

Three studies [17, 19, 20] compared the efficacy of HDP vs lidocaine mixture infiltrations used as placebo. The three studies reported that in both groups there was a statistically significant improvement in pain and function, with an effect in favor of the groups treated with HDP.

Hypertonic dextrose vs hyaluronic acid (HA)

Hashemi et al. [18] compared the efficacy of HDP vs HA intra-articular, reporting equal efficacy in reducing pain and improving function at 3 months of follow-up.

Hypertonic dextrose vs ozone infiltration

Hashemi et al. [22] compared intra-articular infiltration with hypertonic dextrose vs. intra-articular ozone, reporting equal efficacy in reducing pain and improving function at 3-months follow-up.

Hypertonic dextrose vs platelet rich plasma (PRP)

Rahimzadeh et al. [26] compared intra-articular infiltration of Hypertonic Dextrose vs intra-articular PRP and observed statistically significant improvement of pain and function in both groups at 2 and 6 months; nevertheless, at 6 months follow-up, a better effect was observed in the PRP group. Eroglu et al. [23] conducted a similar study, reporting however that the improvement of pain and function did not reach statistical significance in any of the groups.

Hypertonic dextrose vs erythropoietin

Rahimzadeh et al. [21] compared intra-articular infiltration with hypertonic dextrose vs intra-articular infiltration with erythropoietin, they reported pain reduction in both groups at 3 months of follow-up with difference in favor of the erythropoietin group.

Hypertonic dextrose vs radiofrequency

Rahimzadeh et al. [21] compared the effects of intra-articular infiltration with hypertonic dextrose vs intra-articular radiofrequency application. They observed that in both groups there was a statistically significant improvement in pain and function at 3 months of follow-up, without significant differences between groups.

Finally, two studies [24, 25] compared intra-articular hypertonic dextrose application vs subcutaneous dextrose application, reporting that in both groups there was a statistically significant improvement in pain and function.

Discussion

Our main objective was to evaluate the efficacy and safety of prolotherapy with hypertonic dextrose in patients with knee osteoarthritis.

Therapeutic efficacy

Clinical studies have reported favorable effects of HDP for knee OA treatment. Case series studies [27–29] show that HDP application in patients with knee OA promotes pain reduction and improves function during approximately 12 months or longer without generating adverse events; nevertheless, the absence control groups limits the strength of these findings.

Randomized clinical trials [30, 31] have compared HDP vs conservative treatments (physiotherapy, exercise program) in individuals with knee OA and have reported greater efficacy of HDP in terms of reducing pain and

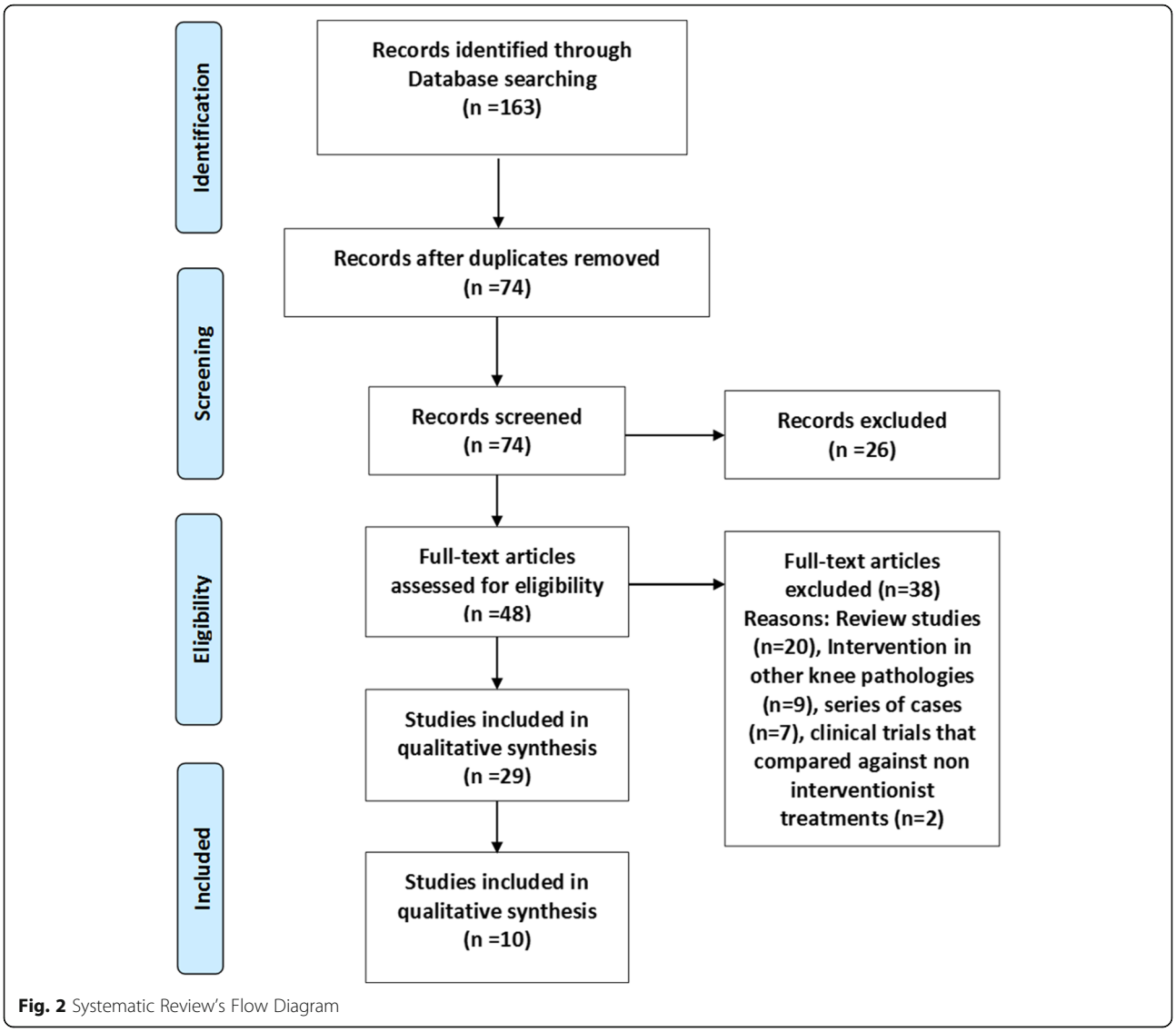

Fig. 2 Systematic Review's Flow Diagram

improving function. When analyzing the effectiveness of HDP in OA knee treatment vs other interventional treatments, HDP appeared to be more effective than local anesthetics [17, 19, 20]. Probably, HDP provides both a short-term analgesic effect based on neurogenic mechanisms [32, 33] and also a long-term analgesic effect via the repairment of soft tissues and cartilage [34, 35].

HDP appears to have the same short-term clinical efficacy as intra articular infiltration with HA [18]. Although it has been documented that HA produces significant improvement in pain and joint function in individuals with knee OA, [36] international guidelines for its use vary considerable, as it is recommended in some countries [6] while in others it is considered to cause more frequent adverse effects than steroids [36]. Based on the above, HDP could be a better alternative than HA for treating patients with knee OA, probably with a better cost-benefit ratio and with the possibility that HDP could also reduce pain of extra joint origin.

When comparing intra articular infiltrations with hypertonic dextrose vs intra articular infiltrations with ozone, it was observed that they had a similar effect in the reduction of pain and short-term improvement of function [29]. It has been reported that intra articular infiltrations with ozone decrease proinflammatory cytokines such as Interleukin 1β and Alpha Tumor Necrosis Factor [37] and modify joint oxidative stress by re-establishing the intra-articular redox balance [38]. Therefore, ozone and HDP could be therapeutically complementary, by decreasing the inflammatory process with ozone at first, followed by a chondrogenic effect of HDP. Studies that combine these interventions are needed to verify this hypothesis.

On the other hand, when comparing intra-articular infiltrations with PRP and HDP, both seemed to have a

Table 1 Design of studies, interventions, evaluations and results

Authors and year of publication, Design	Dextrose group intervention	Control group intervention	Evaluations and Outcomes
Reeves and cols., 2000. [17] 77 patients with OA diagnosis of knee grade II or more of KL, divided into 2 treatment groups.	**Dextrose group**: 35 patients treated with 3 intra-articular infiltrations of 10% hypertonic dextrose, frequency every 2 months.	**Solution Lidocaine group:** 33 patients treated with 3 intra-articular infiltrations of a bacteriostatic water solution + lidocaine, frequently every 2 months.	Pain when walking measured with VAS: **Dextrose** **Lidocaine** Basal 3.94 (2.92) 3.83 (2.20) 6 months 2.56 (1.97) 2.85 (2.20) Pain at standing from a chair measured with VAS: **Dextrose** **Lidocaine** Basal 5.33 (2.80) 5.83 (2.60) 6 months 3.96 (2.68) 4.80(2.91)
Hashemi and cols.,2012 [18] 100 patients with knee OA diagnosis (no mention of grade), divided into 2 treatment groups.	**Dextrose group**: 50 patients treated with 3 intra-articular infiltrations of 2ml of hypertonic dextrose at 25%, with monthly frequency.	**HA group:** 50 patients treated with 5 intra - articular infiltrations of 2 ml of HA, weekly frequency.	Pain measured in the KOOS subscale: **Dextrose** **HA** Basal 44.6(16.8) 45.1(19.8) 3 months 68.8(11.4) 69.8(10.2) Function measured with the KOOS scale: **Dextrose** **HA** Basal 43.2(16.2) 42.2(17.9) 3 months 71.5(12.7) 70.0(11.0)
Rabago and cols., 2013 [19] 90 patients with knee OA diagnosis any grade of KL classification, divided into 3 treatment groups.	**Dextrose group**: 30 patients treated with 3 to 5 intra-articular infiltrations with 6ml. of dextrose at 25% and extra-articular infiltrations of 22.5ml of dextrose at 15% in the insertion of ligaments and tendons, with monthly frequency.	**Saline Solutions + Lidocaine group:** 29 patients treated the same treatment scheme as the Dextrose group, but using a combination of saline solutions + lidocaine. **Exercise group:** 31 patients with home exercise program.	Changes in the WOMAC Pain subscale: **Dextrose** **Saline/ Lidocaine** **Exercise** Basal 66.8(14.9) 66.7 (16.1) 63.2(13.1) 3 months -11.78 (3.62) -5.79 (3.67) -4.89 (3.66) 6 months - 15.50 (3.56) -6.40 (3.63) -8.07 (3.60) 12 months -14.18 (3.62) -7.38 (3.67) -9.24 (3.63) Changes in the total WOMAC scale: **Dextrose** **Saline/ Lidocaine** **Exercise** Basal 63.1(15.5) 62.7 (14.3) 60.5(11.3) 3 months - 13.31 (3.32) -8.19 (3.37) -4.26 (3.36) 6 months -15.85 (3.26) -8.12 (3.33) -8.48 (3.28 12 months -15.32 (3.32) -7.59 (3.36) -8.24 (3.33)
Rabago and cols., 2013 [20] 45 patients with knee OA diagnosis any degree of KL classification, divided into 2 treatment groups.	**Dextrose group**: 27 patients received 3 to 5 intra-articular infiltrations with 6ml. of dextrose at 25% plus extra articular infiltrations of 22.5ml dextrose at 15% with (11 patients) or without (16 patients) 5% sodium morruate, in the insertion of ligaments and tendons, with monthly frequency.	**Control group**: 18 patients who received the same treatment scheme as the Dextrose group, but using a combination of saline solution + lidocaine (9 patients) or a home exercise program (9 patients).	Change in the WOMAC Pain subscale: **Dextrose** **Control** Basal 62.3(12.9) 71.9(13.5) 3 months -11.0(2.8) -3.9(3.1) 6 months -16.5 (3.4) -2.7 (4.3) 12 months -18.1 (3.8) -4.6 (5.0) Changes in the total WOMAC scale: **Dextrose** **Control** Basal 59.9(12.2) 67.0(10.08) 3 months -14.2(2.7) -7.0 (3.4) 6 months -16.2 (3.1) -6.6 (3.6) 12 months - 17.6 (3.2) -8.6 (5.0)
Rahimzadeh and cols., 2014 [21]. 70 patients with OA knee diagnosis grade I to III of KL, divided into 3 treatment groups.	**Dextrose group**: 26 patients treated with an intra-articular infiltration with 5ml. of dextrose at 25%.	**Erythropoietin group**: 20 patients treated with an intra-articular infiltration with 4000 IU of erythropoietin. **Radiofrequency group**: 24 patients treated with an intra-articular pulsed radiofrequency session.	Pain measured with VAS: **Dextrose** **Radiofrequency** **Erithropoietin** Basal 7.11 (1.03) 7.08 (1.41) 6.65 (0.98) 3 months 5.53 (1.6) 5.50(1.93) 3.5(1.23)
Hashemi and cols., 2015 [22]. 80 patients with OA knee diagnosis grade I and II of KL, divided into 2 treatment groups.	**Dextrose group**: 40 patients treated with 3 intra-articular infiltrations of 7ml. of hypertonic dextrose at 12.5%, frequency weekly.	**Ozone group:** 40 patients treated with 3 intra-articular infiltrations of 5-7 ml of ozone at 15 mcg / ml, several times a week.	Pain measured with VAS: **Dextrose** **Ozone** Basal 8.1 (1.1) 7.6 (1.3) 3 months 3.0 (1.2) 2.8(1.1) Function measured with WOMAC Scale: **Dextrose** **Ozone** Basal 58.5(13.3) 56.3(11.5) 3 months 83.7(15.3) 81.6(13.7)
Eroglu and cols.,2016 [23]. 60 patients with OA knee diagnosis grade I - III of KL, divided into 3 treatment groups.	**Dextrose group**: 20 patients received 3 intra-articular infiltrations with 6ml. of hypertonic dextrose plus extra-articular infiltrations of 22.5ml of hypertonic dextrose in the insertion of ligaments and tendons, frequency every 3 weeks.	**PRP group**: 18 patients treated with 3 intra-articular infiltrations of PRP, frequency every 3 weeks. **Saline Solution group (SS)**: 20 patients treated with the same infiltration protocol as the Dextrose group but using 0.09% saline.	Pain measured with VAS: **Dextrose** **PRP** **Saline Solutions** Basal 7.00 (4.20) 6.88(4.22) 7.10 (4.20) 3 months 5.80 (3.38) 6.11(3.14) 6.80 (3.89) 6 months 5.35 (3.39) 6.35 (2.25) 6.90 (4.06) Function measured with WOMAC Scale: **Dextrose** **PRP** **Saline Solutions** Basal 33.50 (13.7) 33.33 (13.6) 32.70 (13.9) 3 months 30.35 (12.0) 30.96 (13.1) 32.35 (13.3) 6 months 30.70 (12.5) 31.16(12.0) 32.12(13.6)
Farpour and cols.,2017 [24]. 52 patients with OA knee diagnosis grade II - III of KL, divided into 2 treatment groups.	**Intra-articular Dextrose group**: 25 patients received 2 intra-articular infiltrations with 6 ml. of hypertonic dextrose at 25%, with intervals of 2 weeks between each infiltration.	**Subcutaneous Dextrose group**: 25 patients received 2 sessions of subcutaneous infiltrations with hypertonic dextrose at 25%, 2 ml in painful points, with intervals of 2 weeks between each session.	Pain measured with VAS: **Intra-articular Dextrose** **Subcutaneous Dextrose** Basal 7.80 (1.70) 7.32 (1.46) 2 months 5.90 (2.69) 5.00 (2.27) Function measured with WOMAC Scale: **Intra-articular Dextrose** **Subcutaneous Dextrose** Basal 45.68 (11.18) 46.52 (14.19) 2 months 39.36 (14.88) 36.44(16.2)
Rezasoltani and cols.,2017 [25]. 104 patients with OA diagnosis of knee grade II - IV of KL, divided into 2 treatment groups.	**Intra-articular Dextrose group**: 54 patients received 3 intra-articular infiltrations with 8 ml. of 10% hypertonic dextrose, a week interval between infiltrations.	**Subcutaneous Dextrose group**: 50 patients received 3 sessions of extra-articular infiltrations with 10% hypertonic dextrose, applying 4 points of 2.5 ml each, around the knee, with a week interval between infiltrations.	Pain measured with VAS: **Intra-articular Dextrose** **Subcutaneous Dextrose** Basal 3.6 (0.4) 3.7 (1.8) 5 months 2.8(0.5) 1.8 (0.9)
Rahimzadeh and cols., 2018 [26]. 42 patients with OA knee diagnosis grade I or II of KL, divided into 2 treatment groups.	**Dextrose group**: 21 patients received 2 intra-articular infiltrations with 7ml. of hypertonic dextrose 25% every 4 weeks.	**PRP group**: 21 patients treated with 2 intra-articular infiltrations of 7ml of PRP, frequency every 4 weeks.	Pain measured with WOMAC subscale: **Dextrose** **PRP** Basal 14.6 (1.4) 14.5 (1.5) 2 months 7.1 (1.7) 5.4 (1.8) 6 months 8.0 (1.6) 6.2 (2.1) Function measured with total WOMAC scale: **Dextrose** **PRP** Basal 67.1 (7.9) 67.9 (7.3) 2 months 34.8 (6.9) 27.1 (9.1) 6 months 38.7(6.6) 31.4 (10.2)

HA, Hyaluronic Acid; KL, Kellgren y Lawrence; KOOS, Injury Scale and Knee Osteoarthritis; OA, osteoarthritis; PRP (Platelet Rich Plasma); VAS, Visual Analogue Scale; WOMAC, OA Index of Eastern Ontario and McMaster University;

similar effect reducing pain and improving function short-term, although less efficiency was observed at medium-term [26]. A recent meta-analysis [7] indicated that the effectiveness of PRP for treating knee OA is based on an increased release of growth factors that favor chondrogenic effects. HDP could be an alternative to PRP for treating knee OA, as PRP application implies a greater technique complexity, higher costs and greater variability in forms of preparation [39]; additionally, HDP could also induce chondrogenic effects [34].

When comparing the efficacy of HDP vs intra articular radiofrequency, equal short-term efficacy was observed [21]. A recent review study [40] mentioned that radiofrequency could be a promising treatment for knee OA given the positive results that have been published, but more prospective studies and long-term monitoring are needed. HDP could be an option of less complexity and a better cost-benefit ratio when compared to radiofrequency for treating knee OA; nevertheless, more studies are needed to evaluate this aspect.

On the other hand, intra articular infiltrations with erythropoietin were more effective than infiltrations with hypertonic dextrose in pain control [21], which was an unexpected outcome; nonetheless, we did not find other studies where this intervention was used in patients with knee OA.

We also analyzed the effectiveness of intra articular hypertonic dextrose vs extra articular hypertonic dextrose. Five studies [17, 18, 21, 22, 26] used the intra articular application of hypertonic dextrose as a single intervention, all of them reported a statistically significant reduction of pain and function improvement for up to 6 months. Furthermore, the series of cases of Eslamian et al. [27] indicated that therapeutic effects of intra articular hypertonic dextrose could be attributed to the chondrogenic mechanisms reported by Topol et al. [34] However, Rabago et al. [20] measured cartilage in individuals with knee OA using magnetic resonance, at one year follow-up they observed symptomatic and functional improvement, but they did not find an increase of the articular cartilage thickness, neither a decrease of speed in cartilage loss.

Other studies have reported similar reduction of pain and function improvement when comparing intra-articular hypertrophic dextrose vs subcutaneous dextrose; [24, 25] this therapeutic effect cannot be attributed to chondrogenic mechanisms or to ligamentous or tendinous remodeling, but perhaps due to neurogenic effects. Two studies [19, 20] combined intra-articular and extra-articular HDP applications on ligaments insertions and tendons and observed a long term effect. This response could be explained by a probable summative effect of the various mechanisms above mentioned.

Previous systematic review and meta-analysis studies [11, 41] reported a greater effect of HDP in reducing pain and improving function of patients with knee OA; however, these reviews included case series studies in their analysis and / or clinical trials compared HDP with non-interventional treatments or placebo injections.

Although our results indicate that HDP has beneficial effect in individuals with knee OA, the studies included in this systematic review have a low methodological quality in their design and present a high risk of bias, which weakens the evidence provided. International clinical guidelines recommend only the use of corticosteroids [5, 6] and / or hyaluronic acid [6] as intra-articular treatment for OA of the knee. Our results do not indicate that HPD should be considered a first-choice treatment for knee OA; more likely, it should be an alternative when treatments with greater evidence have failed.

Duration of therapeutic effect

In relation to the length of the HDP effects when treating knee OA, we found that nine studies [18–26] evaluated results with a follow-up of 2–3 months and all of them reported that the beneficial effect did not end. Six studies evaluated the HDP effects at 5–6 months [17, 19, 20, 23, 26] and five of them observed that the effect lasted the whole time. Whereas two studies [19, 20] evaluated the HDP effects at 12 months and they also observed that the beneficial effect lasted the whole year. Two case series by Rabago et al. [28, 29] also described this favorable effect duration; one of them monitored the patients for 2.5 years and reported that the beneficial effect persisted. Clearly, the benefits of using HDP in individuals with knee OA are long term, for one year or even longer. It should be noted that the effects could last for longer time than the effects produced by corticosteroids, hyaluronic acid [36] and ozone, [10] and could have a similar lasting effect to platelet-rich plasma treatment [7]. Studies with long term follow-ups are needed to confirm this observation.

Dosage

The dosages utilized varied considerably, we found that patients received 1 to 5 doses of HDP, with a mode of 3 doses. The frequency of HDP applications was between once every two months to once a week, with one monthly application as the most commonly used. The concentration of dextrose used in intra-articular applications varied from 10 to 25%, the most frequent was 25%, the volume used per application was of 2 to 8 ml, with a mode of 6 ml. For extra-articular applications, 15% the most common concentration, applied in tendon and ligament insertion, pain points and points corresponding to the emerging knee superficial sensory nerves. The recommended dosage was between 2 to 6 sessions of prolotherapy to achieve the maximum therapeutic benefit, at monthly intervals using dextrose concentrations of 25% for intra-articular treatment and 15% for extra-joint applications [12]. In some of the studies, these

recommendations were not fully met, which could have affected our results.

Action mechanisms

The action mechanisms of Hypertonic Dextrose Prolotherapy (HDP) are still unclear; it has been proposed that hypertonic dextrose can activate inflammatory processes and induce growth factors release in exposed tissues [42, 43]. In animal models hypertonic dextrose increases fibroblast proliferation, collagen production and extracellular matrix in treated ligaments and tendons, [44, 45] and it also generates a trophic effect in articular cartilage [46, 47]. Additionally, a recent study reported that glucose decreased the expression of metalloproteinase 1 [48]. Similar effects have been reported in humans; for instance, Topol et al. [34] studied individuals with severe knee OA through a histological evaluation and 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. [35] reported a decrease in ligamentous laxity in patients with anterior cruciate ligament involvement when treated with hypertonic dextrose. These mechanisms facilitate tissue repair, which could explain the medium and long-term analgesic effects of HDP.

Other mechanisms of action have been proposed to explain the rapid analgesic effect of HDP, involving neurogenic mechanisms such as hyperpolarization of nerve fibers by opening potassium channels [32] or stimulation of the glycine inhibitory receptor, [33] which reduces the nociceptive transmission.

Adverse reactions and / or side effects

Four studies [20, 21, 24, 26] reported that there were no side effects or adverse reactions in patients who received HDP. Two studies [17, 19] reported minimal adverse reactions in both HDP treated groups and control groups, including mild to moderate pain, inflammation and self-limiting hematomas. The rest of the studies did not report whether or not there were side effects and / or adverse reactions. No serious complications such as infections or allergic reactions were observed in any of the studies.

Limitations

The number of studies included in this review is small, and each study itself included a low number of treated patients. Most of the studies included in this systematic review have low methodological quality in their design and present a high risk of bias, which weakens the evidence provided. The dosage used varied considerably among studies, as well as the concentrations of dextrose. Although all studies evaluated the same pathology, the application sites and frequency of application also varied significantly, which may have influenced our results. Similarly, the evaluation and analysis of the results were heterogeneous; even though the use of HDP could help decrease the degenerative process in cartilage, only few studies included radiological follow-up.

Conclusions

According to our results, HDP appears to be more effective for pain reduction and function improvement than infiltrations with local anesthetics; HDP seems to be as effective as HA, infiltrations with ozone and radiofrequency, and less effective than erythropoietin and PRP. The beneficial effects of HDP were observed in the short, medium and long term, reporting duration of the effect up to 1-year follow-up. Nevertheless, these results should be interpreted with reservation, given the low methodological quality and high risk of bias of the studies included, which limits the evidence provided and does not allow solid conclusions; so our findings do not indicate that HDP is a therapeutic agent of first choice for the treatment of knee OA, but it can be considered as an alternative or adjuvant treatment. More studies and better methodological quality are needed to establish a better level of evidence on the efficacy and safety of using HDP in patients with knee OA.

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None.

Authors' contributions

CATZ, PIAV and IEJR conceived and design the study, in addition to drafting the introduction section. MLLN, BGLR and DMR data collection. WBF and TBGC analyzed the results. All authors contributed to the discussion and writing of the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

The study was approved by the Ethical Committee of the "Universidad Juárez Autónoma de Tabasco" in compliance with the ethical principles.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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