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Original Articles

A Comprehensive Update of Prolotherapy in the Management of Osteoarthritis of the Knee

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This is a comprehensive review of the literature focusing on the use of prolotherapy in the treatment of osteoarthritis of the knee. It covers the background, efficacy, and advantages of prolotherapy in the management of osteoarthritis symptoms and then covers the existing evidence of the use of prolotherapy for this purpose. Current treatments for osteoarthritis of the knee are numerous, yet patients continue to endorse chronic pain and poor quality of life. Prolotherapy is a treatment that has been inadequately studied with poor sample sizes and lack of standardization between trials. However, in recent years the literature on prolotherapy in the treatment of knee osteoarthritis has grown. Although there is still a lack of homogeneity, trials have shown that dextrose prolotherapy, autologous conditioned serum, hyaluronic injections, and normal saline administered either intra- or peri-articularly are comparable in reducing pain scores to other primary treatment options. The mechanism of action for prolotherapy is still unclear, but researchers have found that prolotherapy plays some role in cartilage growth or chondrogenesis and has been shown to have improved radiographic outcomes. Prolotherapy appears to be a safe treatment alternative that has been shown to improve stiffness, pain, function, and quality of life in osteoarthritis of the knee. Knee osteoarthritis is remarkably prevalent in the United States and is one of the most common causes of disability in the elderly population. Although there are many treatment options, patients continue to live with chronic pain which can incur high costs for patients. A safe, long-term, and effective solution has not yet been identified. Prolotherapy has been shown to be a safe option for improving pain, function, and quality of life as effectively as other treatment options.

INTRODUCTION

According to the 2017 *Global Burden of Disease* study, osteoarthritis is a leading cause of disability, affecting approximately 303 million people worldwide.[1] It can affect any joint, but primarily affects the knee in 87% of cases. Between 2007 and 2017, osteoarthritis has lead to a 30.8% increase in years lost due to disability.[1] With a growing population of obese and aging individuals, these numbers are only expected to increase in the coming years.[2]

Other risk factors for osteoarthritis include genetic predisposition, gender, trauma, hormones, metabolic syndromes, and chronic joint overload.[3] Over the years, new evidence has shown that the cause of osteoarthritis is multifactorial, moving away from the idea of an entirely degenerative disease of cartilage. Onset of osteoarthritis is influenced by inflammation, joint mechanics, and metabolic responses of joint tissues such as cartilage, ligaments, tendons, bone, adipose, and synovial fluid cells.[3] Osteoarthritis leads to an inability of articular surfaces to absorb and distribute forces adequately, resulting in joint destruction and

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pain.[3] Current treatment options for osteoarthritis of the knee consist of conservative, nonpharmacologic management; pharmacologic therapies such as topical compounds, oral medications, and intra-articular injections; and surgical replacement of the joint for cases refractory to medical management.[4–7]

Of the treatment options, intra-articular injections are popular due to the side effects of oral medications and invasive surgical procedures.[8] Prolotherapy, in particular, has gained much attention since its formal introduction for the treatment of musculoskeletal pain in the 1950s by George Hackett, a U.S. general surgeon.[8–10] Prolotherapy is a form of regenerative therapy whose exact mechanism of action is still unclear.[8] Current propositions include that injected irritants, such as hypertonic dextrose, morrhuate sodium, dextrose/phenol/glycerin solution (DPG), or platelet rich plasma (PRP), into the peri- and intra-articular spaces stimulate growth factor and cytokine production, leading to regeneration of previously damaged ligaments, tendons, and other intra-articular structures.[8,11–13] Various human trials have also been conducted on the use of prolotherapy for different musculoskeletal conditions, with positive results seen for its application in osteoarthritis of the knee.[14–18]

With a large proportion of the world suffering from osteoarthritis, effective treatment for the alleviation of symptoms is important. While conventional treatment for osteoarthritis of the knee involves the use of topical and oral medications, behavioral modifications, and injections, the search for safe, efficacious alternatives for patients who have failed the conventional medical treatment options is imperative to reduce the need for invasive surgical procedures. In this review, we will focus on current treatment options of osteoarthritis, prolotherapy, and emerging evidence on the use of prolotherapy for the treatment of osteoarthritis of the knee.

PROLOTHERAPY INDICATIONS

Prolotherapy has been shown to be successful in treating a variety of musculoskeletal conditions. One major indication for prolotherapy is knee osteoarthritis in patients with chronic knee pain and radiographic findings of Kellgren-Lawrence stages II-IV.[14,19] Based on most recent 2019 ACR guidelines, the use of prolotherapy is in fact recommended against in patients with knee osteoarthritis citing limited number of trials, further complicated by variabilities within the methodology.[6] As recent studies have been promising, with further standardization of the approach to administering prolotherapy, guidelines will likely change to reflect the outcomes of the studies.

Additionally, prolotherapy is also indicated for the treatment of other painful, prolonged conditions, including enthesopathy, tendinosis, and anterior cruciate ligament (ACL) laxity. Prolotherapy can be considered when physical therapy or surgery fails to provide a therapeutic benefit or when patients have an intolerance to NSAIDs, steroids, or opiates. Additionally, any chronic ligament or tendon pain secondary to sprains or strains may be an indication for prolotherapy treatment.[20,21]

TECHNIQUE

Patients with knee osteoarthritis that have been chosen to undergo prolotherapy treatment should first have the knee thoroughly examined by the injector, and the tender locations on the knee should be appropriately marked. Between 0.1% to 0.5% lidocaine is often given prior to administration of the injectate to decrease pain and irritation from the irritant.[22] Extra-articular injections should be performed at the major tendon and ligament insertions of the site of tenderness using a peppering technique. An inferomedial or inferolateral intra-articular approach is preferred as a suprapatellar approach predisposes the patient to accidental collision of the needle against the patella, leading to pain and possible damage to the chondral cartilage of the patella.[23]

Patients may be prescribed acetaminophen and/or a narcotic for pain and should be instructed to avoid taking any nonsteroidal anti-inflammatory medications (NSAIDs). Patients should be advised to rest for at least 2 to 3 days in order to allow time for the knee to heal appropriately.[14] Injection intervals are typically spaced 4-6 weeks apart with individuals averaging between 4 to 6 treatments.[8,20] Improvement in pain and isometric strength may be noticed after the first treatment; although, most patients do not see results until after their second or third treatment.[8,20] If no improvements are seen following three prolotherapy sessions, alternative interventions should be considered.[8]

FORMULATIONS

The most common injectant used in prolotherapy is hypertonic dextrose (D-glucose) 10%, 12.5 %, 16.5%, 20%, and 25%. Injections are diluted with local anesthetics in 1:1, 1:2, 1:3, 1:4, or 2:5 parts. Because dextrose is a normal component of our blood chemistry and can also be administered safely in large doses, it is considered to be an ideal proliferant.[21,24] Some studies have shown that a 25% dextrose solution is most appropriate in the treatment of intra-articular knee injections. If this solution proves to be ineffective, a gradual progression to sodium morrhuate (5%) is recommended.[21] Sodium morrhuate (5%) is composed of 2% benzyl alcohol and sodium salts of cod liver oil. Another common formulation used is a dextrose/phenol/glycerin solution (DPG), consisting of 25% dextrose, 25% glycerin, and 2.5% phenol. DPG solutions are diluted with local anesthetics in a 1:1, 1:2, or 2:3 concentration before injection.[21]

CONTRAINDICATIONS

Prolotherapy is contraindicated if a patient has allergies to anesthetic or proliferative solutions, or the ingredient components. Other contraindications for prolotherapy treatment include acute arthritis, bursitis, tendinitis, gout, complete rupture of a tendon or ligament, or rheumatoid arthritis.[20,21] In addition, prolotherapy should be avoided in patients who have an active infection, cancer, or any other underlying condition that may prolong the healing process or leave the patient immunocompromised. Relative contraindications to prolotherapy include the regular usage

of corticosteroids or NSAIDs, as they counteract the body's inflammatory processes, or current long term use of narcotics, as they lower the body's immune response.[20]

SIDE EFFECTS

Prolotherapy is a very low-risk procedure, and complications are extremely rare. The most common side effect is soreness and swelling at the site of injection after treatment, which usually disappears within 1-2 days. Additional risks include bruising, headaches, allergic reactions, temporary numbness, and nerve irritation.[20] Another less common side effect is the development of an infection following treatment.

CURRENT TREATMENT OPTIONS FOR OSTEOARTHRITIS OF THE KNEE

Chronic osteoarthritis of the knee leads to years of debilitating pain and disability.[1] Current recommendations by the American College of Rheumatology (ACR), the American Association of Orthopedic Surgeons (AAOC), and the Osteoarthritic Research Society Initiative (OARSI) have slight variations in management, but all support early management with exercise and weight loss.[4–6] Studies show that a 7-10% reduction in weight is sufficient for pain relief, improved functionality, and delayed progression of cartilage degeneration.[25,26] In addition to weight loss, regular exercise has also been shown to reduce pain and disability in patients with osteoarthritis.[27,28] Other nonpharmacological treatments include massage therapy and biomechanical interventions, such as braces and walking canes.[6,29]

The use of pharmacological therapies is another mainstay of treatment for osteoarthritis of the knee and is commonly used in conjunction with non-pharmacologic treatments. These include topical treatments, oral medications, and intraarticular injections.[4–6] The use of topical capsaicin relieves osteoarthritic pain by inhibiting the release of substance P from type-C nociceptive fibers, which are responsible for the pain response.[30] The ACR continues to conditionally recommend the use of topical capsaicin, while OARSI guidelines recommend against its use due to poor quality of evidence.[4,6] Topical NSAIDs have also been shown to achieve pain relief equivalent to oral NSAIDs at one year, and due to fewer side effects, it is a good alternative for some patients.[4–6,31] However, many continue to use oral NSAIDs as they are preferred and provide adequate pain relief faster than their topical counterpart.[31] Duloxetine is also recommended for patients with concomitant depression.[4,32] Other oral treatments with differing recommendations are paracetamol and tramadol.[4–6]

After failure of symptom relief with nonpharmacological, topical, and oral treatments, physicians proceed with intra-articular injections. Of the intra-articular injection options, steroids are widely used for short-term treatment of osteoarthritis of the knee.[33,34] However, its use is controversial as studies have shown an increased loss of cartilage volume and worsening radiographic evidence of osteoarthritis with intra-articular steroid injections.[33,35,36] Hence, while ACR and OARSI guidelines have recommendations for intra-articular steroid injections, the AAOS has inconclusive recommendations.[4–6] Additionally, hyaluronic acid, a glycosaminoglycan and major component of synovial fluid, which is decreased in osteoarthritis of the knee, has also been used to help with long-term pain relief for osteoarthritis.[4,37,38] However, ACR and AAOS guidelines recommend against its use.[5,6] Other novel injectable treatment options include biological therapies such as platelet-rich plasma, prolotherapy, and stem cells. As of now, recommendations for these injections are inconclusive due to inadequate evidence.[4–6]

When all conservative measures have been exhausted without adequate pain relief, surgical procedures are the definitive treatment option for severe pain.[7,39] However, even with total joint replacement, up to 20% of patients can have continued symptoms or postoperative dissatisfaction.[7,39,40]

PROLOTHERAPY MECHANISM OF ACTION

Although the mechanism of action of prolotherapy is not entirely clear, there have been many hypotheses proposed to help rationalize its effects. The general concept is that injectectates initiate a local inflammatory response that ultimately trigger a healing cascade. Release of cytokines and growth factors, such as platelet-derived growth factor, transforming growth factor β, epidermal growth factor, insulin-like growth factor, and connective tissue growth factor, promote proliferation of fibroblasts and deposition of collagen deposition, strengthening the joint and reducing pain.[20,21,24]

The most common prolotherapy solutions-hypertonic dextrose, DPG, and morrhuate sodium-are thought to function through different mechanisms. Hypertonic dextrose ruptures local cells via an osmotic gradient; DPG initiates local cellular irritation; and morrhuate sodium draws inflammatory mediators, leading to scarring of pathologic neovasculature.[8] Other alternatives have been proposed, such as the administration of hypertonic dextrose causes the activation of inhibitory glycine receptors, thereby causing hyperpolarization and the reduction of nociceptive transmission.[41] Ultimately, these injectates converge to form larger, stronger collagen fibers that increase joint stability and thus decrease pain.

CLINICAL STUDIES: EFFECTS OF PROLOTHERAPY ON KNEE OSTEOARTHRITIS

Osteoarthritis continues to be a burden on not only those who suffer from it but also healthcare systems and caregivers. A study in Ontario, Canada in 2005 found that participants who reported Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores greater than or equal to 55 had a greater likelihood of incurring osteoarthritis-related costs, and those costs were three times greater than participants with WOMAC total scores less than 15.[42] Several treatment options are currently available, and there are novel interventions being researched around the world; however, there continues to be a debate surrounding which options are the most efficacious in the

management of osteoarthritis. Thus, the need to provide therapeutic interventions that can help abate that burden that are not only safe but also cost-effective is imperative.[11]

A variety of studies have been done to assess the efficacy of prolotherapy on knee osteoarthritis. However, many of those studies have been found to provide low quality evidence due to data heterogeneity.[11,43,44] Prolotherapy has been found to be associated with a favorable side effect profile, high patient satisfaction, and improved knee-specific quality of life and could provide an alternative to pain-relief medications and more invasive surgical interventions such as knee replacement for the management of knee osteoarthritis.[11,45] The low-quality evidence in support of prolotherapy for the treatment of osteoarthritis has resulted in its classification as a complementary therapeutic intervention. This has led to further attempts to determine if prolotherapy has similar or superior therapeutic efficacy compared to alternative treatments in the treatment of osteoarthritis.[46]

A blinded, randomized control trial in Hong Kong compared intra-articular hypertonic dextrose prolotherapy (containing 25% dextrose) with normal saline injection.[47] They found that both the normal saline and dextrose prolotherapy groups had improved WOMAC pain scores at 52 weeks compared to baseline but, the dextrose prolotherapy group had statistically significant improvement in WOMAC pain score compared to the normal saline group.[47] The study also found that dextrose prolotherapy resulted in significantly improved visual analogue scale (VAS) scores for knee pain at 52 weeks compared to normal saline.[47] Previous studies have shown similar effects. A study at the University of Wisconsin found that when dextrose prolotherapy was compared to normal saline injections and home exercise programs, dextrose prolotherapy had a significantly greater improvement in WOMAC composite and knee pain scale scores from baseline at 52 weeks, however, this study used both intra-articular 25% dextrose and extra-articular 15% dextrose prolotherapy techniques.[14] A randomized prospective placebo-controlled study with 68 participants in 2000 found significant improvement in knee pain as well in knees treated with dextrose prolotherapy (containing 10% dextrose) compared to those treated with an injection of .075% lidocaine in bacteriostatic water or active solution.[48]

Several studies have also been conducted to determine if the injection method of dextrose prolotherapy could have an impact on the effectiveness of prolotherapy in knee osteoarthritis. A randomized clinical trial published in 2017 compared intra- and periarticular 25% dextrose prolotherapy in fifty-two adults with knee osteoarthritis.[49] They concluded that both intra- and periarticular dextrose prolotherapy resulted in significant improvement from baseline in VAS, Oxford knee scale (OKS), and WOMAC scores at eight weeks.[49] There was no significant difference between the two different methods, suggesting that either can be used in the treatment of knee osteoarthritis.[49] This is consistent with findings of a 2015 prospective study in which intra-articular 20 % dextrose prolotherapy resulted in significant improvement of total WOMAC scores.[50]

Interestingly, a randomized clinical trial in 2017 found a significantly greater improvement in VAS scores at five months in participants treated with periarticular prolotherapy compared to those treated with intra-articular prolotherapy.[51] Interestingly, in 2012 a prospective study with 36 participants found that those who received both intra- and extra-articular dextrose prolotherapy reported significant improvement in WOMAC and KPS scores at 52 weeks in the treated knee, as well as a significant improvement of KPS scores in the untreated knee.[52] Similarly, a two-arm controlled trial with 128 participants published in 2016 reported that intra-articular dextrose prolotherapy alone, as well as intra- and periarticular dextrose prolotherapy in combination, led to significant improvements in WOMAC and VAS scores from their respective baseline and when compared to physiotherapy alone.[53] Additionally, they reported that those who received both intra- and periarticular dextrose prolotherapy achieved not only faster improvement in WOMAC and VAS scores but significantly better improvement in WOMAC and VAS throughout the year.[53] Effectiveness of periarticular prolotherapy could possibly be explained by periarticular healing effects, where inflammatory response around the joint enhance blood perfusion to the capsular joint and thus to the cartilaginous tissue for regeneration, or by a concept similar to neural prolotherapy, where injection of dextrose promote treatment of damaged subcutaneous nerves closer to the skin.[51]

Intra-articular injection of platelet-rich plasma is a possible regenerative treatment option for the management of knee osteoarthritis.[11] A double-blind, randomized clinical trial with 42 participants in 2018 compared the effects of intra-articular platelet-rich plasma and intra-articular 25% dextrose prolotherapy.[54] Similar trends for both groups were observed in all outcomes measured, with peak improvement happening within eight weeks, followed by an insignificant decline by 24 weeks.[54] They found that both platelet-rich plasma and dextrose prolotherapy significantly improved WOMAC scores over six months; however, they also observed that the improvement in WOMAC scores was greater in those treated with platelet-rich plasma than those treated with dextrose prolotherapy.[54]

In contrast, a randomized placebo-controlled trial in 2016 found that while both platelet-rich plasma and dextrose prolotherapy resulted in improvement of measurements of pain and function, the improvement was not significant in either group.[55] A randomized clinical trial with 92 patients published in June of 2020 also found no significant improvement in WOMAC scores in those treated with 50 % dextrose prolotherapy.[56] They also found no significant difference in VAS scores for knee pain intensity in the dextrose prolotherapy group compared to baseline and compared to those treated with platelet-rich plasma at one month and six months.[56] The study revealed that at one month, there was no significant improvement in WOMAC scores compared to baseline in those treated with platelet-rich plasma; however, by six months, the WOMAC scores in the platelet-rich plasma group had significantly improved compared to baseline.[56] Both the 2018 and the 2020 studies determined that the WOMAC improvements seen in the platelet-rich plasma group were significantly better compared to the dextrose prolotherapy group at one month and six months.[54,56]

Autologous conditioned serum (ACS) is a relatively newer option for the possible management of knee osteoarthritis.[56] A randomized clinical trial comparing the efficacy of intra-articular autologous conditioned serum, platelet-rich plasma, and 50% dextrose prolotherapy in 92 patients with knee osteoarthritis found that VAS pain scores were significantly improved in the group receiving autologous conditioned serum at one month and six months compared to the dextrose prolotherapy group.[56] WOMAC scores were also significantly improved in the autologous conditioned serum group at six months compared to baseline, in contrast to the insignificant difference found in the dextrose prolotherapy group.[56] The study also reported that compared to those treated with dextrose prolotherapy, participants that were treated with autologous conditioned serum experienced a significantly better improvement in WOMAC scores at one month and six months.[56]

A randomized clinical trial in 2019 with 120 participants compared the effects of intra-articular 20% dextrose prolotherapy on Knee Injury and Osteoarthritis Outcome Score (KOOS) and VAS scores to the effects of intra-articular botulinum neurotoxin injections, intra-articular hyaluronic acid injections, and physical therapy.[16] Researchers concluded that when used individually, botulinum neurotoxin, dextrose prolotherapy, and physical therapy all led to a reduction in KOOS and VAS scores at the end of the study with no significant difference in the reduction in either KOS or VAS between the dextrose prolotherapy group and either the botulinum neurotoxin group or the physical therapy group.[16] Intra-articular dextrose prolotherapy was found to have a significantly greater improvement in KOOS and VAS scores when compared to intra-articular hyaluronic acid; however, this was also seen in comparisons of intra-articular hyaluronic acid to both physical therapy and intra-articular botulinum toxin injections.[16] The study found that intra-articular dextrose prolotherapy and intra-articular botulinum toxin injection displayed similar efficacy in improving scores of stiffness, pain, daily function, sports function, and quality of life. Though, scores on symptom abatement were more significantly improved in the botulinum toxin group than the dextrose prolotherapy group.[16]

A randomized clinical trial, with 80 participants, in 2015 compared the efficacy of intra-articular 12.5% dextrose prolotherapy to intra-articular ozone prolotherapy in patients with knee osteoarthritis and found that both treatments resulted in significant improvements in WOMAC scores at three months with no significant difference between the two groups.[57] A double-blind, randomized clinical trial with 70 participants published in 2015 compared intra-articular 25% dextrose prolotherapy to treatment options such as intra-articular erythropoietin and intra-articular radiofrequency ablation found similar evidence for the ability of both intra-articular dextrose prolotherapy and the other treatment options to significantly improve pain at three months with no significant difference between groups.[58]

Some research has been done to investigate the disease-modifying ability of dextrose prolotherapy in knee osteoarthritis. Using radiographic data taken at 0 months and 12 months after treatment with intra-articular 10% dextrose prolotherapy, researchers assessed osteophyte grade, cartilage thickness, distal femur width both proximal and distal to the intercondylar notch, and proximal tibial width.[48] Radiographic evidence revealed stability of eleven out of thirteen variables studied, as well as a significant improvement in the final two variables, lateral patellofemoral cartilage thickness and distal femur width.[48] In contrast, a clinical trial in 2013 used magnetic resonance imaging to evaluate changes in cartilage volume after 52 weeks in participants treated with dextrose prolotherapy and found no significant difference in the percent of cartilage volume lost compared to participants who received normal saline prolotherapy.[59] However, they did find a correlation between change in cartilage volume and WOMAC pain subscale score in the dextrose prolotherapy group that was not present in the normal saline participants.[59] Soliman et al. in 2016 used plain radiographs and ultrasound to obtain measurements of the medial collateral ligament, lateral collateral ligament, and patellar tendon dimensions as well as cartilage thickness and reported a similar effect.[53] Participants that were treated with both intra- and periarticular dextrose prolotherapy, as well as those treated with only intra-articular dextrose prolotherapy, had significant improvements in ligament and tendon dimension and cartilage thickness at 12 months.[53] Another study in 2016 discusses the association between intra-articular dextrose prolotherapy and chondrogenesis, in which histologic evidence of cartilage growth was observed in participants with grade IV osteoarthritis of the knee and exposed subchondral bone following treatment with intra-articular prolotherapy with 12.5% dextrose.[60]

While the studies referenced in this section provide evidence for the efficacy of intra-articular dextrose prolotherapy in effectively managing pain and possibly modifying disease in knee osteoarthritis, they are not without their individual limitations. The differences in outcome measurements, dosages, and quality of data make definitive conclusions difficult.[44,46,61,62] Study design is variable, with some being randomized clinical trials, prospective randomized clinical trials, some with the use of blinding, others without, variable arm numbers, and variable use of controls. Population characteristics such as baseline WOMAC scores, degree of severity of osteoarthritis, gender, average age, average BMI, activity level, and previous treatments received vary considerably between studies. In addition, many studies have insufficient sample sizes, making generalization problematic. Studies had differences in injection dosages, injection schedule, number of injections, the concentration of injection substrate, and method of administering injections. Outcome measurements and follow-up times varied in many of the studies.

As mentioned in several other reviews concerning the efficacy of hypertonic dextrose prolotherapy, there is still a need for larger clinical trials with a standardized treatment regimen and long term follow up in order to accurately determine the efficacy of treatment.[44,46,61] However, findings consistently show improvement in the quality of life, coupled with a minimal amount of reported adverse reactions. This suggests that hypertonic dextrose prolotherapy could be used as an alternative treatment in patients suffering from osteoarthritis that have failed to improve following treatment with more conservative or other pharmacologic treatments for osteoarthritis.

CONCLUSION

The current treatment of knee osteoarthritis is early management, including a variation of exercise, weight loss, muscle strengthening, and pain relief with NSAIDs or corticosteroid injections. With the projected increase in the number of individuals suffering from osteoarthritis of the knee, finding long-term treatment options that are safe and satisfactory in providing relief of symptoms is crucial to decrease the need for surgical procedures and improve quality of life. A review of current randomized controlled trials on the efficacy of prolotherapy in treating osteoarthritis of the knee reveals that prolotherapy is a promising treatment option.

Most frequently, studies have administered 3-4 injections approximately 4 weeks apart. By 8 weeks, improvements in VAS and other objectives outcomes are noted compared to baseline and these effects are shown to persist up to assessment at even 52 weeks following the first injection. The majority of trials have focused on different concentrations of dextrose administered intraarticularly. Going forward, there will need to be further standardization of the methods of administering periarticular prolotherapy if used in combination with intraarticular prolotherapy. In addition, there will also need to be further studies comparing other forms of injectate compared to dextrose, such as PRP, ozone, erythropoietin to name a few.

Numerous clinical trials show significant improvement of osteoarthritic pain of the knee without any significant side effects reported following the use of prolotherapy. Although there is heterogeneity between studies with regard to study variables, the results consistently show significant improvement in radiographic outcomes, pain scores, and quality of life with prolotherapy treatment. Prolotherapy appears to be a safe and effective alternative to physical therapy, surgery, NSAIDs, steroids, and opiates when they fail to provide clinical relief. Since osteoarthritis is a chronic condition, further studies with extended follow-up periods evaluating long-term effects of prolotherapy are also needed to fully assess its efficacy and long-term sequelae. This field of regenerative therapy would benefit from larger, standardized, long-term studies to gain further insight into treating osteoarthritis of the knee.

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Table 1. Clinical Effectiveness

Author (Year)	Design of study	Outcome measurements	Groups Studied and Intervention	Results and Findings	Conclusions
Farpour and Fereydooni [49] (2017)	RCT/ 2-arm	OKS WOMAC: - pain - stiffness - function - total VAS	52 adults between the ages of 38-70 with primary KOA for at least 3 months. Randomly allocated into groups of 25 (2 participants dropped due to personal reasons) to receive either intra- articular (6 ml of 25% dextrose) or periarticular (6 ml of 25% dextrose) injections of dextrose prolotherapy. Two injections were given in a two-week interval.	VAS, OKS, and WOMAC scores after dextrose prolotherapy improved from 7.32±1.46 (VAS), 23.52±7.77 (OKS), and 46.52±14.19 (WOMAC) at baseline to 5.00±2.27, 28.36±9.62, and 36.44±16.2 at 8 weeks in the periarticular injection group (p<0.001). VAS, OKS, and WOMAC scores in the intra-articular group also improved from 7.80±1.70 (VAS), 24.72±7.13 (OKS), and 45.68±11.18 (WOMAC) at baseline to 5.90±2.69, 27.76±8.67, and 39.36±14.88 at eight weeks (p<0.001). No significant difference in any outcome measurement between the two groups.	Dextrose prolotherapy, either by peri- or intra-articular injection can be used in the management of KOA. Periarticular injection seems to be more easily performed by healthcare professionals, and less painful than other management options.
Rahimzadeh et al. [54] (2018)	RCT/ 2-arm	WOMAC: - Composite - functional limitation - pain level - stiffness	42 patients between the ages of 40-70 with stage 1 or 2 KOA. Randomly allocated into groups of 21 to receive intra-articular injections of either 7mL of platelet-rich plasma or 7mL 25% dextrose. Injections given at 0 months and 1 month.	In both groups the overall WOMAC score at 6 months was significantly decreased compared to baseline. WOMAC decreased in the PRP group from 67.9±7.3 at baseline to 31.4±10.2 at 6 months (P<0.001). WOMAC decreased in the DPT group from 67.1±7.9 at baseline to 38.7±6.6 at 6 months (P<0.001).	Both PRP injections and DPT can be used to reduce pain and improve quality of life in patients with mild KOA.
Pishgahi et al. [56] (2020)	RCT/3 arms	WOMAC VAS	92 patients between the ages of 40-75 with KOA. Randomly allocated into groups of 30 (DPT), 30 (PRP), and 32 (ACS) to receive 50 % dextrose prolotherapy, platelet-rich plasma, or autologous conditions serum (ACS). Dextrose injections were given once a week over a three-week	VAS scores in the ACS group showed significant improvement at 6 months compared to the dextrose and PRP groups (P<0.001). WOMAC scores in the dextrose group at one month and 6 months were significantly less improved than those measured in the PRP and ACS groups (p<0.001). WOMAC scores in the ACS group at one	ACS therapy could potentially be used as an alternative to PRP therapy or DPT to effectively reduce pain and improve knee function long term in patients with KOA.

Author (Year)	Design of study	Outcome measurements	Groups Studied and Intervention	Results and Findings	Conclusions
			period. PRP and ACS injections were given twice every seven days.	month and 6 months were significantly improved compared to the dextrose group (p<0.001). No significant difference in the WOMAC scores of the ACS and PRP groups at one month and 6 months (p=0.999)	
Rezasoltani et al. [16] (2020)	RCT/4 arms	Primary: VAS pain Secondary: KOOS	120 patients 50 years of age and older with KOA. Randomly assigned to one of four groups: Physical therapy group- superficial heat, transcutaneous electrical nerve stimulation, and pulsed ultrasound Botulinum neurotoxin group- one intra-articular injection of botulinum neurotoxin type A Hyaluronic acid group- injections of hyaluronic acid given 3 times weekly Dextrose prolotherapy group- injections of 20% dextrose given 3 times weekly	Effects on VAS and KOOS score were significantly less in the hyaluronic acid group compared to all other groups (P<0.05). VAS scores were significantly improved in the botulinum neurotoxin group compared to the physical therapy group (P=0.015). No statistically significant reduction in KOOS scores of the botulinum neurotoxin and dextrose groups compared to physical therapy.	Botulinum toxin and dextrose prolotherapy combined with exercise can both be used to effectively control pain over several months in patients with KOA. While physical therapy alone was not as effective at reducing pain compared to botulinum toxin and dextrose, its effects on KOOS scores were comparable suggesting a benefit for patients with KOA.

Author (Year)	Design of study	Outcome measurements	Groups Studied and Intervention	Results and Findings	Conclusions
Sit et al. [47] (2020)	RCT/ 2 arm	Primary: WOMAC pain score at 52 weeks Secondary: WOMAC - composite - function - stiffness VAS knee pain Physical function EuroQol-5D score	76 patients between the ages of 45-75 years old with KOA from general outpatient clinics in Hong Kong. Randomly allocated into 2 groups of 36 and received either DPT (5 ml of 25% dextrose) or NS (5 ml of normal saline) injections at weeks 0, 4, 8, and 16.	Difference-in-difference estimates revealed favorable outcomes on: The WOMAC pain score at 52 weeks: -10.34 (-19.20 to -1.49, *P* = 0.022) points. WOMAC function score: -9.55 (-17.72 to -1.39, *P* = 0.022) WOMAC composite score: -9.65 (-17.77 to -1.53, *P* = 0.020) VAS pain intensity score: -10.98 (-21.36 to -0.61, *P* = 0.038) EuroQol-5D VAS score of 8.64 (1.36 to 5.92, *P* = 0.020). No statistical difference found in physical function tests or medication use (*P*= 0.350)	Compared to normal saline, dextrose prolotherapy improved measurements of pain, function, and quality of life in patients with KOA

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