Acta Scientific Orthopaedics (ISSN: 2581-8635)

Volume 5 Issue 7 July 2022

Review Article

Current Clinical Considerations in the Use of Dextrose Prolotherapy in Sport and Exercise Medicine

Mark Wilson[1], Anna Topping[1]*, Nirmala Perera[1], Richard Saw[1], David Hughes[1] and Stephan Praet[2]

[1]Sports Medicine, Australian Institute of Sport, Bruce ACT, Australia

[2]Ochre Health Medical Centre, Health Hub, Bruce ACT, Australia

***Corresponding Author:** Anna Topping, Sports Medicine, Australian Institute of Sport, Bruce ACT, Australia.

DOI: 10.31080/ASOR.2022.05.0490

Received: February 25, 2022

Published: June 08, 2022

Abstract

Introduction: Prolotherapy is an injection-based therapy used for multiple acute and chronic musculoskeletal pain drivers. The aim of this clinical discussion is to review the clinical considerations in the use of prolotherapy in sport and exercise medicine. We will also compare intervention options and provide valuable clinical pearls.

Methodology: The focus of this clinical discussion is on the application of prolotherapy in clinical practice.

Summary: it is hoped that this narrative review guides clinicians on possible uses of prolotherapy in clinical practice, based on the current evidence of efficacy, complications and risk profile. The integration of clinical experience, combined with a review of the best evidence in the field, may assist in clinical decision making.

Keywords: Dextrose Prolotherapy; Sport; Exercise; Medicine

Introduction

Prolotherapy is an injection-based therapy used for multiple acute and chronic musculoskeletal pain drivers. Initially developed 80 years ago as a method to treat various chronic musculoskeletal conditions [1], the technique was formalised by Dr George Hackett in the 1950s in the US [1-3]. Commonly used injectates (proliferants) are hypertonic dextrose, isotonic dextrose, normal saline, morrhuate sodium and ozone, and combinations thereof [5]. The focus of this paper is dextrose prolotherapy, as its popularity has increased in recent years. There are multiple techniques through which dextrose can be administered to local tissues, but in general, a dextrose solution is administered via a standard injection technique into superficial or deep soft tissues. Dextrose can be injected into small and large joints.

Despite its popularity, there is limited evidence for its efficacy in many conditions. There are more studies being produced, but most are of low quality, and difference in the substance injected limits study comparison. Consequently, it is challenging for clinicians to interpret the current evidence to guide how, when and if they should use prolotherapy in clinical practice.

The aim of this clinical discussion is to examine current clinical considerations in the use of prolotherapy in sport and exercise medicine.

Safety profile

Aside from occasional local soft tissue irritation and bruising, the risk of infection is low and does not have a higher risk profile compared to the injection or local anaesthetics or corticosteroids [32]. Dextrose is a physiological fluid and does not have the risk profile of injectable medications. Infection is rare but has been described in case reports [33]. There is no high-level evidence demonstrating a higher risk of infection with dextrose prolotherapy compared to other commonly used injectates. Dextrose prolotherapy is 'steroid-sparing' and may therefore avoid issues related to immunosuppression, particularly in diabetics. There is no evidence suggesting that dextrose is a higher risk injectate in small and large joint injections than local anaesthetics, cortisone or saline.

Contraindications

The contraindications for dextrose prolotherapy include the presence of active infection, known allergy to dextrose, previous hypersensitivity or other adverse local reactions or underlying medical conditions which compromise healing potential [34,35]. Rheumatoid arthritis and active gout are also contraindications, especially if the clinician targets an actively involved joint. Concurrent use of oral steroids or NSAIDs is also a contraindication when using dextrose prolotherapy, as these agents inhibit the healing response of soft tissues [10,36].

Proposed mechanism of action

Prolotherapy is thought to induce an inflammatory reaction to promote soft tissue healing [8]. The precise mechanism of action of dextrose prolotherapy is multifactorial. Hyperosmolar dextrose dehydrates cells at the injection site until they rupture by creating a large osmotic gradient. This starts an acute inflammatory process, followed by a healing response [9]. The process is cellularly-driven and relies on granulocytes and macrophages. The acute inflammation and the subsequent regenerative phase are intricately linked at a cellular and molecular level; the coupled dynamics of this process highlight the inherent healing capacity of injured soft tissue when placed under stress. Inflammatory cytokines, including interleukins, prostaglandins, thromboxanes, and leukotrienes regulate the cellular environment that controls the reparative phase [10].

It has been theorised that periarticular injections or deposition of hypertonic dextrose into painful entheses decreases joint laxity and articular dysfunction, improves overall biomechanics and decreases pain [10,11]. When used in high concentrations, dextrose acts as a local osmotic cellular stressor along a concentration gradient, which drives an augmented inflammatory response, necrosis and then, regeneration of soft tissue components [12]. Dextrose also has direct analgesic effects, especially in its isotonic preparation. This direct analgesic effect suggests less of an inflammatory mechanism of action and more of a direct neurogenic effect at the nociceptor level [13].

Prolotherapy and hydrodissection

In addition to the role of dextrose as a possible pain modulator, a technique called perineural injection therapy relies on the role of hydrodissection and the mechanical effect of relieving local or regional sites of superficial nerve compression (typically sensory nerves), especially in transition zones and between anatomical compartments bordered by fascia [5,11,14]. This is considered the Lyftogt approach [14].

Dextrose and its therapeutic effect at different concentrations

Work has been done to explore the mechanism of action of different concentrations of dextrose prolotherapy [18]. The typical clinical use ranges of dextrose solutions are 5%-25%, although the use of higher concentrations has been described. Traditional prolotherapy is based on the theory of tendon and ligament regeneration by injecting > 10% dextrose to stimulate local inflammation. The higher concentration preparations are associated with more deleterious effects on nerve form and function, that is, it is directly neurotoxic [19]. At lower concentrations, it has been demonstrated that isotonic dextrose has the capacity for direct analgesic effects [13,20].

The induction of a sublethal insult, followed by a rapid cellular response appears to be pro-inflammatory in nature; this may be the key molecular step in the purported regenerative process of hypertonic dextrose prolotherapy. The high extracellular concentration of dextrose leads to a state of non-enzymatic glycosylation, whereby glucose binds to extracellular matrix components and attenuates the resorption of extracellular matrix (ECM) for tissue remodelling [21,22]. These positive remodelling effects have been seen in both *in vivo* and human clinical studies in relation to increases in tendon and ligament strength and stiffness, as determined by an improved modulus of elasticity [23]. Furthermore,

light microscopy and electron microscopy studies of human posterior sacroiliac ligaments three months following prolotherapy have shown an increase in the number of active fibroblasts and collagen density, with an average increase of collagen fiber diameter of more than 50% [24].

In addition to these effects on tissue healing and regeneration, there is an upregulation of inflammatory mediators, including COX-2, IL-1, IL-6, TNF alpha and VEGF after treatment with hypertonic dextrose [22,25]. In association with this, there is a strong decrease in TGF-beta bioactivity after proliferant treatment. Cell migration analysis has also revealed that dextrose prolotherapy decreases tenocyte migratory capacity and that the decreased cellular activity was seen at 24 hours, but that after this period, there is a tendency towards tissue regeneration as the acute inflammatory response becomes gradually attenuated over time [9,26].

Comparing dextrose prolotherapy with other interventions

Research groups have explored the utility of hypertonic dextrose solutions for inducing fibrosis and the mechanisms by which this occurs [37]. Phenol works more as a direct tissue irritant, which subsequently oxidises into quinine groups, leading to cellular damage and necrosis [38]. The implicated mechanism of action is direct cellular damage, subsequent necrosis, potentiation of the inflammatory milieu with interleukins and other cellular mediators of acute inflammation and then subsequent cellular-driven healing via tenocytes, myofibroblasts and other cell lines, involving signalling mechanisms that are not yet fully elucidated.

Dextrose prolotherapy vs platelet rich plasma

The efficacy of dextrose prolotherapy has been compared to traditional platelet rich plasma (PPR) for plantar fasciitis [39]. Both treatments were effective for chronic, recalcitrant plantar fasciitis, expanding the treatment options for patients for whom conservative care has failed. In terms of a foot functional index score, there was an improvement with both PRP and dextrose prolotherapy, but PRP demonstrated superiority. Indeed, for pain, there was a 30.4% improvement with PRP and a 15.1% improvement with dextrose prolotherapy. The study concluded that although PRP treatment may lead to a better initial improvement in function compared with dextrose prolotherapy, the longer-term benefits are not significantly different. Further research is needed to clarify these results and the role of dextrose prolotherapy for plantar fasciitis as an additional treatment option. Another study suggested a significant decrease in the overall WOMAC score of patients who undergo either PRP therapy or dextrose prolotherapy for knee OA [39].

There is reasonable pilot-level evidence supporting the use of dextrose prolotherapy, polidocanol, autologous whole blood and PRP injections in the treatment of lateral epicondylosis [40]. In follow-up periods ranging from 9 to 108 weeks, there were statistically significant ($p < 0.05$) improvements in pain score measures and disease-specific questionnaires. In relation to lateral epicondylosis, CSI has been shown to have short term benefit only and is not superior to other injection modalities and physiotherapy in the long-term (Lai., *et al*. 2018). Furthermore, CSI has been shown to be non-superior to placebo in the long-term, possibly because lateral epicondylosis is largely a self-limiting condition (Aljawadi., *et al.* 2019).

Patients need to be well informed about the best available evidence what therapeutic options may be applicable to them. A discussion with the patient about the risks, benefits, short and long-term clinical efficacy of the myriad treatment modalities is essential when deciding on a treatment pathway. In this context, given that dextrose prolotherapy has a very low risk profile and may result in cost savings in an increasingly strained healthcare sector, it may serve a suitable role.

Prolotherapy vs. corticosteroid injection

In relation to the efficacy of prolotherapy vs. corticosteroid injection for the treatment of chronic lateral epicondylosis, a prospective, randomized controlled, double-blinded study involving 24 subjects with clinically determined chronic lateral epicondylosis was performed [41]. It was determined that both prolotherapy and corticosteroid injection were well tolerated and provided long-term clinical benefit, with no significant difference between groups. Another group recruited 30 subjects with chronic lateral epicondylosis and assigned them into two groups: hypertonic dextrose or methylprednisolone injection. All subjects were assessed through VAS scores and Quick DASH scores at baseline and after one- and three-months' follow-up [42]. Again, both interventions were effective in the short-term treatment of chronic lateral epicondylosis, but dextrose prolotherapy was more effective than steroid injection at the three-month follow-up; whether these clinical benefits were sustained was not determined.

Dextrose prolotherapy vs NSAIDS

To best of our knowledge, there is no current evidence available to compare efficacy of dextrose prolotherapy vs. NSAIDS. This is an area that requires further research.

Dextrose prolotherapy and specific clinical conditions

A recent systematic review examined the efficacy of dextrose prolotherapy in the treatment of chronic musculoskeletal pain [10]. Electronic databases PubMed, Healthline, Omni Medical Search, Medscape, and EMBASE were searched from 1990 to January 2016. Prospectively designed studies that used dextrose as the sole active prolotherapy constituent were selected. The quality of evidence was assessed using the Physiotherapy Evidence Database assessment scale for randomised controlled trials (RCTs) and the Downs and Black evaluation tool for non-RCTs. Fourteen RCTs, one case-control study and 18 case series met the inclusion criteria and were evaluated. Pain conditions were categorised into tendinopathies, osteoarthritis, spine/pelvic and myofascial pain. It was determined that prolotherapy is superior to controls in Osgood–Schlatter disease, lateral epicondylosis of the elbow, traumatic rotator cuff injury, knee OA, finger OA and myofascial pain.

Of interest, in a small case control-study, dextrose prolotherapy has been shown to be beneficial in recalcitrant medial tibial stress syndrome (MTSS) [12], complementing the clinical experience of one of the authors (MW). From this systematic review, the use of hypertonic dextrose prolotherapy is supported for the treatment of tendinopathies, knee and finger joint OA and spinal/pelvic pain due to ligament dysfunction [54]. Efficacy in acute pain, as first-line therapy, and in myofascial pain cannot be determined from the literature, and more research is needed to delineate the purported benefits.

Dextrose prolotherapy in the management of back pain

In chronic lower back pain patients, a relatively swift analgesic effect has been described within 15 min following injection of a buffered D5W solution into the epidural space using a vertical caudal epidural technique [13]. Eighty-four percent (16/19) of dextrose recipients and 19% (3/16) of saline recipients reported a statistically significant pain reduction of ≥ 50% pain at four hours. These findings suggest a neurogenic effect of 5% dextrose on pain at the dorsal root level.

In relation to the sacroiliac joint, a Korean group conducted a prospective, randomized, controlled trial that compared intra-articular prolotherapy with triamcinolone acetonide injection using fluoroscopic guidance, with a bi-weekly schedule and maximum of three injections [43]. It was found at follow-up that prolotherapy provided significant pain relief. Although the duration of effect was longer than that achieved in the steroid injection group, further studies are needed to confirm the safety of this intervention and to validate an appropriate injection protocol for clinicians.

Dextrose prolotherapy in the management of peripheral nerve lesions

Despite research, it is still unclear what drives the clinical benefits of perineural prolotherapy. Is it the direct cellular effects outlined previously and supported in the literature? Are the benefits in association with 'nerve lesions' due to a direct mechanical effect of the dextrose injectate, that is, a neural hydrodissection effect, where there may be the added benefits of soft tissue decompression, freeing up the passage of a superficial nerve or the expansion/liberation of tight fascial bands which constrict a nerve's local blood supply (vaso nervosum)? These direct mechanical effects have been described in the literature with a host of other injectates and whether 5% dextrose adds additional clinical utility requires further exploration [44,45]. Furthermore, the effects of hydrodissection may not be isolated to small sensory or cutaneous nerves.

Given our limited understanding of dextrose perineural injection therapy, future well-designed trials are necessary to investigate the true effect of hydrodissection, especially at the nerve-fascial interface. Indeed, besides the mechanical effects, the possible biologic action of 5% dextrose is thought to be the reduction in neurogenic inflammation through the inhibition of transient receptor potential vanilloid receptor-1 (TRPV1) that is found in high concentrations in peripheral nerves [46,47]. The attenuation of TRPV1 may then block the release of neuropeptides that supply the inflammatory cascade that drives pain generation. One study demonstrated a significant reduction in the cross-sectional area of the median nerve compared with that in control groups, namely, perineural injection with normal saline [48]. A single US-guided injection of 5ml of 5% dextrose into the carpal tunnel was shown to be superior to placebo (saline) and lasted for at least six months. This observation suggests that there is an additional anti-neurogenic inflammation mechanism with 5% dextrose, although addi-

tional randomised clinical trials would be best placed to delineate this specific effect.

More recently, another high quality RCTs in carpal tunnel syndrome patients was published. There were clinical improvements in nerve conduction velocity, nerve swelling/cross sectional area and functional outcome during the first three months and this was found to be equivalent to corticosteroid (triamcinolone) injection; the D5W group had a significantly better lasting effect for up to six months [49].

Although these two RCTs [48,49] can be considered evidence-based 'proof-of-principle' studies for other nerve entrapment syndromes, high-quality clinical trials on perineural dextrose injections for more subtle fascial nerve entrapment syndromes are still warranted. The direct, causal relationship between glucose and C-fibre activity in modulating neurogenic inflammation and stabilising the 'inflammatory perineural environment' remains incompletely understood. Nevertheless, as no major adverse outcomes have been described in the literature, perineural injection therapy using buffered isotonic D5W appears to be a safe and an equally effective alternative for injectables containing saline, local anaesthetics or corticosteroids.

Dextrose prolotherapy in the management of arthritis

Regarding he management of athletes with established knee arthritis, recent work has compared the efficacy of intraarticular injections of hyaluronic acid (HA) versus dextrose in combination with periarticular prolotherapy in the management of recreational athletes with knee pain [50]. A total of 54 patients who had chronic knee osteoarthritis (OA) were included in the study. One group involved intraarticular hyaluronic acid combined with periarticular prolotherapy; another group consisted of intraarticular dextrose combined with periarticular prolotherapy. Clinical efficacy and pain were evaluated via the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at pre-treatment and one, three and six-month follow-up. It was found that both groups had a statistically significant improvement in their WOMAC and VAS scores compared with baseline.

When the two groups were compared, however, the VAS and WOMAC scores in the first month follow-ups were significantly better in the intraarticular dextrose combined with periarticular prolotherapy group, while sixth month follow-up scores were significantly better in the intraarticular hyaluronic acid combined with periarticular prolotherapy group. From this recent study, it can be concluded that both injections are efficacious and safe in treating knee OA, but that the combination of modalities is strongly clinician dependent [50]. These outcomes support the findings of a previous review which found that dextrose injections decreased pain in osteoarthritis patients but did not exhibit a positive dose–response relationship following serial injections [32]. Indeed, dextrose prolotherapy was found to provide a better therapeutic effect than exercise alone, local anaesthetic blocks and cortisone injections when examined at six months following the initial prolotherapy injection.

Knee joint OA is one of the major presentations to Sport and Exercise Physicians and is a source of major source of disability owing to pain and loss of function. One group compared the efficacy of intraarticular corticosteroids and prolotherapy for relieving pain in patients with knee OA. In a randomized, double-blind comparative study on 56 patients with knee OA, a direct comparison was made between these two interventions [51]. It was identified, that at baseline, the mean VAS score of the prolotherapy group was 6.71 ± 0.94, whereas for the steroid group it was 6.36 ± 0.99, which were comparable (P = 0.166). However, after six months, the mean VAS score in the prolotherapy patients was 4.07 ± 1.44 as compared to 3.14 ± 0.89 in the corticosteroid group, with the difference being statistically significant (P = 0.009) in favour of intraarticular corticosteroids, but again, no significant adverse events were identified in the prolotherapy group.

A cost-effective analysis would be useful in this setting. One recent systematic review assessed randomized clinical trials that evaluated therapeutic interventions in patients with knee OA. A comparison was made of the effect of intra-articular vs., extra-articular injections of hypertonic dextrose vs. the effect of intra-articular or extra-articular infiltrations of other substances or interventional procedures in relation to pain and physical function. In terms of pain reduction and function, prolotherapy with hypertonic dextrose was more clinically effective than injections with local anaesthetics, as effective as infiltrations with hyaluronic acid, ozone or radiofrequency ablation, but less effective than PRP; beneficial effects were observed in the short, medium and long term. However, given that no side effects or major adverse events were identified in the patients treated with hypertonic dextrose, this treatment modality both clinically useful and cost-effective [52].

Dextrose prolotherapy in the management of shoulder pain

Prolotherapy has also been used for shoulder sporting injuries, especially rotator cuff tears and tendinopathy [53]. Studies have examined the effectiveness of periarticular/neurofascial hypertonic dextrose prolotherapy, as compared to conventional physiotherapy, for the treatment of chronic rotator cuff tendinopathy in the short to medium term [54,55]. The evidence for this approach is mixed, but one recent RCT recruited 66 patients with chronic rotator cuff tendinopathy [53]. Outcomes were assessed, namely, a change in shoulder pain intensity and functional loss, using an objective measure (the Shoulder Pain and Disability Index); these outcomes were recorded and compared between the two intervention groups (prolotherapy versus physiotherapy). In relation to the physiotherapy cohort, patients received a combination of a structured, supervised exercise program consisting of 10 sessions of 30min duration for three weeks; in addition to this, the physiotherapy group also received multimodal therapies in the form of the application of heat, transcutaneous electrical nerve stimulation (TENS) and pulsed ultrasound.

The prolotherapy cohort received periarticular injections of 8ml of 12.5% dextrose combined with 40mg of 2% lidocaine (mixed in the one preparation). This hypertonic dextrose/LA mixture was injected at weekly intervals; the focus of the injection therapy was to target tender points about the shoulder, especially along the distribution of the suprascapular nerve. It was found that neurofascial dextrose was more effective than physiotherapy in the reduction in pain scores at two weeks and were similar at three months after the conclusion of the respective interventions; the difference in results at two weeks were statistically significant [53]. In relation to functional improvements, dextrose prolotherapy was more efficacious than physiotherapy at two weeks and three months, with a statistically significant difference detected. Beyond three months, the effects of physiotherapy appeared to be more sustained. From this RCT, which built on previous work, and is of good quality, it can be concluded that both interventions are effective for the short-term management of chronic rotator cuff tendinopathy. Combining both modalities is likely to enhance the effectiveness of therapy and improve outcomes, especially in the medium to long-term.

One Australian group identified that in a cohort of shoulder pain patients, the level of pain with overhead activities was significantly reduced at the three-month follow-up in their prolotherapy group and at the six-month follow-up for both their prolotherapy and corticosteroid groups [56]. Furthermore, there were no significant between-group differences at any time point. Therefore, in terms of rotator cuff tendinopathy and symptoms of shoulder impingement, both dextrose prolotherapy and corticosteroid injections were well tolerated and efficacious; however, dextrose prolotherapy offered no additional benefit over subacromial corticosteroid injection for supraspinatus tendinopathy, but it was relatively comparable in relation to pain and functional outcomes.

Dextrose prolotherapy in the management of facial pain

There have been other indications for hypertonic dextrose prolotherapy, aside from the direct sports medicine applications. One group examined the role of the technique for temporomandibular joint dysfunction, a cause of jaw pain [57]. This group assessed the efficacy and longer-term effectiveness of dextrose prolotherapy injections. Their study design was in the form of an RCT and was conducted over three years. Forty-two participants (with 54 joints) meeting temporomandibular dysfunction criteria were randomised (1:1) to three monthly intra-articular injections (20% dextrose/0.2% lidocaine or 0.2% lidocaine) followed by as-needed dextrose/0.2% lidocaine injections through one year. Primary and secondary outcome measures included scores for facial pain and jaw dysfunction; these outcomes were well quantified by applying the concept of maximal interincisal opening (MIO), measured in millimetres. It was concluded that intra-articular dextrose injection for this indication resulted in substantial improvement in jaw pain and function compared with masked control injection at three months; clinical improvements persisted for 12 months and satisfaction was high. This outcome supported the findings of two previous studies, suggestive of a clear clinical benefit [58,59].

Despite research, it is still unclear what drives the clinical benefits of perineural prolotherapy. Is it the direct cellular effects outlined previously and supported in the literature? Are the benefits in association with 'nerve lesions' due to a direct mechanical effect of the dextrose injectate, that is, a neural hydrodissection effect, where there may be the added benefits of soft tissue decompression, freeing up the passage of a superficial nerve or the expansion/liberation of tight fascial bands which constrict a nerve's local blood supply (vaso nervosum)? These direct mechanical effects have been described in the literature with a host of other injectates and whether 5% dextrose adds additional clinical utility requires

further exploration [43-45]. Furthermore, the effects of hydrodissection may not be isolated to small sensory or cutaneous nerves.

Given our limited understanding of dextrose perineural injection therapy, future well-designed trials are necessary to investigate the true effect of hydrodissection, especially at the nerve-fascial interface. Indeed, besides the mechanical effects, the possible biologic action of 5% dextrose is thought to be the reduction in neurogenic inflammation through the inhibition of transient receptor potential vanilloid receptor-1 (TRPV1) that is found in high concentrations in peripheral nerves [46,47]. The attenuation of TRPV1 may then block the release of neuropeptides that supply the inflammatory cascade that drives pain generation. One group demonstrated a significant reduction in the cross-sectional area of the median nerve compared with that in control groups, namely, perineural injection with normal saline; this observation suggests that there is an additional antineurogenic inflammation mechanism with 5% dextrose, although additional randomised clinical trials would be best placed to delineate this specific effect [48]. In relation to other nerve entrapment syndromes, high-quality clinical trials on perineural dextrose injections are still warranted. The direct, causal relationship between glucose and C-fibre activity in modulating neurogenic inflammation and stabilising the 'inflammatory perineural environment' remains incompletely understood. Nevertheless, as no major adverse outcomes have been described in the literature, perineural injection therapy using buffered isotonic dextrose appears to be a safer and equally effective alternative for injectables containing saline, local anaesthetics or corticosteroids for a host of musculoskeletal pain drivers [49,50].

The role of dextrose prolotherapy in chronic pain management

According to a recent randomised double-blind controlled trial, 5% dextrose prolotherapy provided appreciable relief for radicular low back pain and its effects endured for as long as one year [13]. Moreover, it was demonstrated that the analgesic and neurogenic influence of 10 mL volume 5% dextrose on pain with epidural injections and subcutaneous injections was reproducible, safe and had a low complication rate. Older, but well-designed studies have demonstrated that 5% dextrose has an effect in reducing hyperalgesia, allodynia and neurogenic/neuropathic pain at the dorsal root level, but the mechanism is not clear [60,61].

Conclusion

Prolotherapy is an injection-based therapy for acute and chronic musculoskeletal pain and has a long history of clinical use. The two main forms of dextrose prolotherapy utilise isotonic or hypertonic preparations and are considered to work via different mechanisms. Hypertonic dextrose is the most commonly used injectate and has an excellent safety profile. Isotonic dextrose can provide reliable and reproducible analgesia, given the correct patient and indication. Indeed, the application of isotonic dextrose in a perineural injection technique fashion has proven benefit for myofascial disorders, including small and large nerve entrapment syndromes. As a therapeutic intervention, dextrose prolotherapy is a powerful tool in the sports medicine armamentarium. Further investigation with high-quality randomised controlled trials with non-injection control arms in studies specific to sports injuries is needed to determine the efficacy of prolotherapy in achieving good long-term outcomes.

Bibliography

1. Hackett GS. "Joint stabilization through induced ligament sclerosis". *Ohio State Medical Journal* 49 (1953): 877-884.

2. Hackett GS., *et al.* "Ligament and Tendon Relaxation Treated by Prolotherapy". Oak Park: Gustav A. Hemwall (1993).

3. Hackett GS and Huang TC. "Prolotherapy for sciatica from weak pelvic ligaments and bone dystrophy". *Clinical Medicine (Northfield, Il)* 8 (1961): 2301-2316.

4. Rabago David MD., *et al.* "A Systematic Review of Prolotherapy for Chronic Musculoskeletal Pain". *Clinical Journal of Sport Medicine* 15.5 (2005): E376.

5. Dean Reeves K., *et al.* "Short Term Analgesic Effects of 5% Dextrose Epidural Injections for Chronic Low Back Pain: A Randomized Controlled Trial". *Anesthesia and Pain Medicine* 7.1 (2016): e42550.

6. Reeves KD and Hassanein K. "Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity". *Alternative Therapies in Health and Medicine* 6.2 (2000): c68-80.

7. Wheaton MT and Jensen N. "The Ligament Injury-Osteoarthritis Connection: The Role of Prolotherapy in Ligament Repair". *Journal of Prolotherapy* 3.4 (2011): 790-812.

8. Ekwueme EC., *et al.* "Prolotherapy induces an inflammatory response in human tenocytes *in vitro*". *Clinical Orthopaedics and Related Research*® 475.8 (2017): 2117-2127.

9. Hauser RA., *et al.* "A systematic review of dextrose prolotherapy for chronic musculoskeletal pain". *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders* 9 (2016): CMAMD-S39160.

10. Fullerton BD. "Prolotherapy for the thoracolumbar myofascial system". *Physical Medicine and Rehabilitation Clinics of North America* 29.1 (2018): 125-138.

11. Padhiar N., *et al.* "The effectiveness of prolotherapy for recalcitrant medial tibial stress syndrome: a prospective case series". *Journal of Foot and Ankle Research* 14.1 (2020): 32.

12. Maniquis-Smigel L., *et al.* "Short-term analgesic effects of 5% dextrose epidural injections for chronic low back pain: A randomized controlled trial". *Anesthesia and Pain Medicine* 7.1 (2016): e42550.

13. Lyftogt J. "Subcutaneous prolotherapy for Achilles tendinopathy: The best solution?" *Australasian Musculoskeletal Medicine* 12.2 (2007): 107.

14. Lam KHS., *et al.* "Ultrasound-Guided Nerve Hydrodissection for Pain Management: An Updated Review of Anatomy and Techniques". *Journal of Pain Research* 13 (2020): 1957-1968.

15. Stecco C and Schleip R. "A fascia and the fascial system". *Journal of Bodywork and Movement Therapies* 20.1 (2016): 139-140.

16. Klingler W., *et al.* "Clinical relevance of fascial tissue and dysfunctions". *Current Pain and Headache Reports* 18.8 (2004): 439.

17. Trescot A. "Everything old is new again: New developments in prolotherapy". *Techniques in Regional Anaesthesia and Pain Management* 19.1-2 (2015): 14-18.

18. Osborne MD., *et al.* "Nonsurgical Interventions". In *The Hip and Pelvis in Sports Medicine and Primary Care* (2017): 251-279.

19. Conaway E and Browning B. "Neural prolotherapy for neuralgia". *Journal of Prolotherapy* 6 (2014): e928-931.

20. Güran Ş., *et al.* "Dextrose solution used for prolotherapy decreases cell viability and increases gene expressions of angiogenic and apoptotic factors". *Gulhane Medical Journal* 60.2 (20018).

21. Zügel M., *et al.* "Fascial tissue research in Sport and Exercise medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement". *British Journal of Sports Medicine* 52.23 (2018): 1497.

22. Cusi M., *et al.* "The use of prolotherapy in the sacroiliac joint". *British Journal of Sport and Exercise Medicine* 44.2 (2010): 100-104.

23. Klein RG., *et al.* "Proliferant Injections for Low Back Pain: Histological Changes of Injected Ligaments and Objective Measurements of Lumbar Spine Mobility Before and After Treatment". *Journal of Neurological and Orthopaedic Medicine and Surgery* 10 (1989): 123-126.

24. Bordoni B., *et al.* "New proposal to define the fascial system". *Complementary Medicine Research* 25.4 (2018): 257-262.

25. Chung MW., *et al.* "Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth? A systematic review and meta-analysis". *Medicine* 99.46 (2020).

26. Schleip R., *et al.* "Fascia is able to actively contract and may thereby influence musculoskeletal dynamics: a histochemical and mechanographic investigation". *Frontiers in Physiology* 10 (2019): 336.

27. Schleip R., *et al.* "Needle biopsy-derived myofascial tissue samples are sufficient for quantification of myofibroblast density". *Clinical Anatomy* 31.3 (2018): 368-372.

28. Wilke J and Krause F. "Myofascial chains of the upper limb: a systematic review of anatomical studies". *Clinical Anatomy* 32.7 (2019): 934-940.

29. Schleip R and Klingler W. "Active contractile properties of fascia". *Clinical Anatomy* 32.7 (2019): 891-895.

30. Pipelzadeh MH and Naylor IL. "The *in vitro* enhancement of rat myofibroblast contractility by alterations to the pH of the physiological solution". *European Journal of Pharmacology* 357.2-3 (1998): 257-259.

31. Hung CY., *et al.* "Comparative effectiveness of dextrose prolotherapy versus control injections and exercise in the management of osteoarthritis pain: a systematic review and meta-analysis". *Journal of Pain Research* 9 (2016): 847.

32. Bourget-Murray J., *et al.* "A rare case of Haemophilus parainfluenzae septic knee following prolotherapy injections". *Journal of Clinical Orthopaedics and Trauma* 10 (2019): S193-S196.

33. Dan Y and Jing Z. "Dextrose prolotherapy induces the proliferation of new cells to repair soft tissue and to alleviate pain: current status and problems". *Chinese Journal of Tissue Engineering Research* 23.23 (2019): 3754.

34. Rabago D and Nourani B. "Prolotherapy for osteoarthritis and tendinopathy: a descriptive review". *Current Rheumatology Reports* 19.6 (2017): 34.

35. Rotunno A., *et al.* "Corticosteroids in sports-related injuries: Friend or Foe". *South African Family Practice* 58.6 (2015): 28-33.

36. Reeves KD., *et al.* "Dextrose prolotherapy: a narrative review of basic science, clinical research, and best treatment recommendations". *Physical Medicine and Rehabilitation Clinics* 27.4 (2016): 783-823.

37. Siadat AH and Isseroff RR. "Prolotherapy: Potential for the Treatment of Chronic Wounds?" *Advances in Wound Care* 8.4 (2019): 160-167.

38. Kim E and Lee JH. "Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis". *PM and R* 6.2 (2014): 152-158.

39. Rabago D., *et al.* "A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma". *British Journal of Sports Medicine* 43.7 (2009): 471-481.

40. Carayannopoulos A., *et al.* "Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial". *PM and R* 3.8 (2011): 706-715.

41. Bayat M., *et al.* "Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial". *Orthopedic Research and Reviews* 11 (2019): 167.

42. Kim WM., *et al.* "A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain". *The Journal of Alternative and Complementary Medicine* 16.12 (2010): 1285-1290.

43. Dwivedi S., *et al.* "Utility of prolotherapy for upper extremity pathology". *The Journal of Hand Surgery* 44.3 (2019): 236-239.

44. Dufour E., *et al.* "Ultrasound-guided perineural circumferential median nerve block with and without prior dextrose 5% hydrodissection: a prospective randomized double-blinded noninferiority trial". *Anesthesia and Analgesia* 115 (2012): 728-733.

45. Thor JA., *et al.* "Perineural injection therapy in the management of complex regional pain syndrome: a sweet solution to pain". *Pain Medicine* 18.10 (2017): 2041-2045.

46. Poitras T., *et al.* "Selective sensory axon reinnervation and TRPV1 activation". *Molecular Neurobiology* 56.10 (2019): 7144-7158.

47. Wu YT., *et al.* "Six-month efficacy of perineural dextrose for carpal tunnel syndrome: a prospective randomized double-blind controlled trial". *Mayo Clinic Proceedings* 92 (2017): 1179-1189.

48. Wu YT., *et al.* "Randomized double-blinded clinical trial of 5% dextrose versus triamcinolone injection for carpal tunnel syndrome patients". *Annals of Neurology* 84.4 (2018): 601-610.

49. Erdem Y., *et al.* "Comparison of Intraarticular Injections of Hyaluronic Acid versus Dextrose Applied with Periarticular Prolotherapy in the Treatment of Recreational Athletes with Knee Osteoarthritis". *Turkish Journal of Sport and Exercise Medicine* 55.1 (2020).

50. Singh S., *et al.* "A Comparative study of intra-articular injection of steroid versus prolotherapy for pain relief in patients of osteoarthritis knee". *Indian Journal of Pain* 33.1 (2019): 25.

51. Arias-Vázquez PI., *et al.* "Prolotherapy for knee osteoarthritis using hypertonic dextrose vs other interventional treatments: systematic review of clinical trials". *Advances in Rheumatology* 59 (2019).

52. Mofrad MK., *et al.* "Periarticular Neurofascial Dextrose Prolotherapy Versus Physiotherapy for the Treatment of Chronic Rotator Cuff Tendinopathy: Randomized Clinical Trial". *JCR: Journal of Clinical Rheumatology* (2020).

53. Bertrand H., *et al.* "Dextrose Prolotherapy Versus Control Injections in Painful Rotator Cuff Tendinopathy". *Archives of Physical Medicine and Rehabilitation* 97.1 (2016): 17-25.

54. Seven MM., *et al.* "Effectiveness of prolotherapy in the treatment of chronic rotator cuff lesions". *Orthopaedics and Traumatology: Surgery and Research* 103.3 (2017): 427-433.

55. Cole B., *et al.* "Ultrasound-guided injections for supraspinatus tendinopathy: corticosteroid versus glucose prolotherapy-a randomized controlled clinical trial". *Shoulder and Elbow* 10.3 (2018): 170-178.

56. Louw WF., *et al.* "Treatment of temporomandibular dysfunction with hypertonic dextrose injection (prolotherapy): a randomized controlled trial with long-term partial crossover". *In Mayo Clinic Proceedings* 94.5 (2019): 820-832.

57. Rammelsberg P., *et al.* "Longitudinal outcome of temporomandibular disorders: a 5-year epidemiologic study of muscle disorders defined by research diagnostic criteria for temporomandibular disorders". *Journal of Orofacial Pain* 17.1 (2003).

58. Refai H., *et al.* "The efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial". *Journal of Oral and Maxillofacial Surgery* 69.12 (2011): 2962-2970.

59. Kim SR., *et al.* "Critical review of prolotherapy for osteoarthritis, low back pain, and other musculoskeletal conditions: a physiatry perspective". *American Journal of Physical Medicine and Rehabilitation* 83 (2004): 379-389.

60. Yelland M., *et al.* "Prolotherapy injections for chronic low back pain: results of a pilot comparative study". *Australian Association of Musculoskeletal Medicine* 5 (2000): 20-30.

61. Lai WC., *et al.* "Chronic lateral epicondylitis: challenges and solutions". *Open Access Journal of Sports Medicine* 9 (2018): 243.

62. Aljawadi A., *et al.* "The effectiveness of corticosteroid injections in the management of lateral epicondylitis review of literature". *Journal of Orthopedics and Muscular System Research* (2019).