
Prolotherapy as an intervention for chronic, refractory musculoskeletal pain

To the Editor,

Proliferative injection therapy or prolotherapy, also called regeneration therapy, is an interventional modality used for various chronic painful musculoskeletal conditions. Prolotherapy involves a small volume of local anesthetic injections with or without a sclerosing or irritant agent into the connective tissues between the ligament or tendon and bone, or intra-articular space. These injections can be repeated based on the requirement. The mechanism of the

action of prolotherapy is postulated as by activation of an inflammatory response at the site of the injection, increasing levels of growth factors after injections as a result of which there will be regenerative processes in cells in the vicinity. It is also postulated that there is stimulation of fibroblast and vascular proliferation, deposition of dense collagen, and cartilage growth around the area of injection. This modality has not become very popular because it is used as the last weapon from the armamentarium of pain physicians when all other therapies like medications, various other interventional

Table 1: Table depicting systematic review and meta-analysis prolotherapy as an effective intervention in various chronic musculoskeletal pain syndromes

Authors/Year	Indication	Number of Studies	Number of Patients	Key Points
Hauser <i>et al.</i> (2016) ^[6]	Chronic musculoskeletal pain	14 RCTs, 1 case-control study, and 18 case series	1662	Dextrose prolotherapy appears to be efficacious and should be considered as a treatment for pain and dysfunction associated with chronic musculoskeletal conditions, particularly tendinopathies and OA
Krstičević <i>et al.</i> /2017 ^[11]	Osteoarthritis	7 RCTs	393	Data are preliminary, require high quality data
Arias-Vázquez <i>et al.</i> /2019 ^[7]	Knee osteoarthritis	10 RCTs	328 patients received dextrose prolotherapy	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 platelet-rich plasma and erythropoietin
Chung <i>et al.</i> /2020 ^[8]	Tendinopathy, fasciopathy, and ligament injuries	10 studies	358	Insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries
Bae <i>et al.</i> 2021 ^[2]	Chronic musculoskeletal pain	10 studies	750	Dextrose prolotherapy was more effective in the treatment of chronic pain compared to saline injection or exercise

procedures, and other alternative therapies have failed. The existing literature is heterogenous, has a small sample size, is not adequately powered, and is in the form of case reports/series.^[11]

There are several published papers in which prolotherapy was successfully used in managing chronic pain due to various etiologies like knee osteoarthritis, Achilles tendinopathy, coccygodynia, lateral epicondylitis, degenerative disk disease, low back pain, plantar fasciitis, and chronic sacroiliac joint pain.^[2] Various solutions are used for injections in prolotherapy. Although hyperosmolar dextrose (15–25%) is the most commonly used solution, other agents like morrhuate sodium and phenol-glycerin-glucose (P2G) have also been used for prolotherapy.

Johnston *et al.*^[3] used P2G for prolotherapy in cultured murine MC3T3-E1 cells. The authors demonstrated that there was an upregulation of the cartilage cell proliferation enhancer cytokine FGF-2, suggesting an independent effect of P2G. In a randomized controlled trial by Rabago *et al.*,^[4] the authors compared dextrose prolotherapy in 90 patients with chronic knee osteoarthritis with control as saline and home exercises. Interventions were performed on 1st, 5th, and 9th week using 15–25% dextrose solution. On analysis, the authors concluded that there was a more sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with saline injections and at-home exercise. The authors recommended dextrose prolotherapy in patients who were refractory to all other conservative modalities for managing pain due to chronic osteoarthritis. Later, Rabago *et al.* performed prolotherapy in 38 patients with moderate-to-severe knee osteoarthritis using extra-articular injections of 15% dextrose and 5% morrhuate sodium at the peri-articular tendon and ligament

insertions.^[5] Along with this, they also performed a single intra-articular injection of 6 mL 25% dextrose through an inferomedial approach. The injections were performed at 1, 5, and 9 weeks and later the patients were followed up. On analysis, the authors concluded that injections using the above-mentioned approach resulted in safe, significant, and sustained improvement of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-based knee pain, function, and stiffness scores compared to the pain at the baseline. Table 1 summarizes the recent systematic review and meta-analysis published, which has reviewed the existing data and given their verdict.

At present, there is no formal training program for becoming a prolotherapist. Pain physicians, orthopedic surgeons, podiatrists, and primary care physicians are performing the interventions. The scope of learning and practicing prolotherapy is by reviewing the available literature, understanding the injection techniques by attending workshops and courses, selecting the patient appropriately, and following up with the patient so as to know the benefits, harm, or any adverse effects due to the injections done.

To conclude, at present, the evidence of prolotherapy being an effective intervention in chronic musculoskeletal pain appears anecdotal and is not supported by a robust, adequately-powered randomized controlled trial. However, the intervention is indeed safe and has provided relief when all evidence-based, multimodal approaches failed in allaying pain. Well-designed studies with less heterogeneity are required to further explore the scope of prolotherapy.

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Conflicts of interest

There are no conflicts of interest.

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