

The review of dextrose Prolotherapy for several painful musculoskeletal diseases and its possible mechanisms

Wei-Che Hsu MD, Shih-Hsuan Chen MD, MS

Abstract

Musculoskeletal diseases are common causes of chronic pain, they severely impair the patients' quality of life. An aging population could lead to enormously large number of patients diagnosed with musculoskeletal diseases. Management of musculoskeletal diseases can be surgical or non-surgical. Surgical modalities include tissue repair, a joint replacement surgery, and so forth. With the rising cost surgical procedures, the financial burden of health care may be growing, and the quality of life among general populations will be affected eventually.

Dextrose Prolotherapy is another cost-effective treatment option. Avoiding surgical intervention and with lower cost, some cases reported clinically significant improvement with dextrose Prolotherapy. However, the actual mechanism of dextrose Prolotherapy is yet not totally clear. Most investigators proposed that by injection at least 10% dextrose into tendon or ligament insertions, inflammatory process will be induced, proliferation of various cells at injection site will be noted and finally healing of the injured structures will take place. Some other investigators found that dextrose injections below a 10% solution directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction. Both mechanisms mentioned above could reduce the pain severity and improve the daily activity and quality.

This review focus on dextrose Prolotherapy on some common painful musculoskeletal diseases, the research evidence, and its possible explanations.

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Introduction

Painful musculoskeletal diseases may be major causes that affect our quality of life. A wide spectrum

of musculoskeletal diseases inducing pain include tendinopathies, degenerative diseases and trauma to some ligament or cartilage. For the elderly people, it takes longer time to recover from the injuries. Since

Department of Anesthesiology, Chung Shan Medical University Hospital, Taichung, Taiwan

*Corresponding author: Shih-Hsuan Chen, Department of Anesthesiology, Chung Shan Medical University Hospital, Taichung, Taiwan

Tel: + 886- 4-24739595 #

Email: chen.shih.hsuan@gmail.com

population aging is a global phenomenon, there will be even higher incidence of musculoskeletal diseases and will be associated with significantly increased medical expenses. For example, up to 21 million Americans are affected by osteoarthritis (OA) in 1990[1] and the estimated number is projected to increase to nearly 67 million by 2030.[2]

Management of musculoskeletal diseases can be surgical or non-surgical. By 2030, the demand for musculoskeletal surgeries including primary hip and knee replacements are projected to grow substantially, to 0.57 and 3.48 million procedures, respectively.[3] Sadly, any musculoskeletal injury may result in chronic pain even after surgical management. The patients' activities of daily living and quality of life then were affected severely. Health care costs for painful musculoskeletal diseases are obviously rising, thus contributing to greater economic burden and poorer quality of life, since the patients affected by the diseases may lose their jobs and normal activities.

Prolotherapy was first standardized and reviewed in clinical application by Dr. George Hackett in the 1950s. [4] Prolotherapy is an injection technique introducing small amounts of solution into painful ligaments or tendon insertions, trigger points, or the adjacent joint spaces to induce healing of the injured structures. Dr. Gustav Hemwall was another pioneer in the field of Prolotherapy. He continued Dr. Hackett's work after his death in 1969 and trained the majority of the physicians who practiced the technique over the next 30 years. Hence the designation Hackett-Hemwall dextrose Prolotherapy[5]. In 1974, Dr. Hemwall presented his case series of 2,007 Prolotherapy patients to the Prolotherapy Association, the treatment result was promising, more than 99 percent of the patients who completed treatment with Prolotherapy found relief from their chronic pain![6]

In many cases, Prolotherapy treatments provide equivalent outcomes and are less expensive when compared with surgical interventions. Many substances or solutions such as platelet rich plasma (PRP), glycerin or dextrose are used for Prolotherapy injection. While allergic reaction to platelet-rich plasma is reported,[7] dextrose seems to be an ideal solution. Dextrose is the name of a simple sugar that is made from corn and is chemically identical to blood sugar; it is water soluble; it can be safely administered into human bodies, i.e., into multiple areas and with a large amount. Dextrose is also the cheapest proliferant, and it is easily to be prepared. In this review article we will focus on dextrose Prolotherapy. The effects of dextrose Prolotherapy on some common painful musculoskeletal diseases, the research evidence, and its possible mechanisms will be examined.

The Possible Biological Explanations for Dextrose Prolotherapy

There are several hypotheses for biological explanations of Prolotherapy, yet no consensus was reached till now. Those proposed involve the injection of an irritant material into a previously damaged muscle or tendon. Currently, many solutions are reported in Prolotherapy injections, for example, dextrose, P2G (dextrose, phenol, glycerin), platelet rich plasma, stem cell, lipoaspirate, etc. Dextrose was the most commonly proliferant.

Oftentimes, the injected concentration of dextrose ranges from 12.5~25%.[8] Most reports suggest that at least 10% of dextrose is necessary to create an inflammatory process.[9] There are three stages to complete the treatment process of dextrose Prolotherapy: healing stage, proliferation stage and maturation stage.

The first healing stage consists of three overlapping

phases: inflammatory, proliferative with granulation and remodeling with contraction.[10] In this first stage, inflammatory response is induced by high concentration of dextrose and leads to a cytokine cascade and chemotaxis of inflammatory cells including macrophages, platelets, TGF, and growth factors. It usually takes about one week.[11] The second proliferation stage lasts almost 6 weeks. The increase of myofibroblasts, fibroblasts and endothelial cells at injection site happens in this stage. We will find tendon hypertrophy, more extracellular matrix, fibroblastic proliferation and the repair of cartilage defects.[12] It maybe also induce enhanced chondrogenesis by upregulating aggrecan expression via the PKC α -p38-miR141-3p signaling pathway.[13] It then facilitates the formation of type I and type III collagen and strengthening the new connective tissue and joint stability. Finally, it reduces pain and improves function. The third maturation stage lasts months or even one year after the injection. The newly formed type I and type III collagen link continuously and further strengthen soft tissue. The new, stronger and more physiological tissue persists and finally presents its effects to improve clinical outcome.

Interestingly, some other studies suggest that using lower concentration of dextrose may also be effective. Hauser et al.[14] pointed out that a normal human cell contains only 0.1% glucose[15]. When the cells are exposed to increased glucose concentration, even as little as 0.5% dextrose, cell protein synthesis, DNA synthesis, and cell volume will all be increased, and cell proliferation will be noted. The authors concluded that dextrose Prolotherapy is presumed to work by several mechanisms, when the injected dextrose solutions were below 10%, they directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction.

Earlier animal studies noticed that elevated glucose(25 mM, or 4.5%) could lead to both hypertrophic and hyperplastic effects in porcine vascular smooth muscle cells.[16] When human endothelial cells were exposed to high glucose(25 mM, or 4.5%) and hyperosmolarity, increased endothelial transforming growth factor(TGF)-beta1 secretion and bioactivity were also noted.[17] All these findings contributed to the clinical usage of dextrose solutions less than 10% as possible effective proliferants.[18.19]

Disease-based Studies of Dextrose Prolotherapy Temporomandibular joint (TMJ) disorders.

TMJ disorders is an unstable joint disease. It is associated with pain, headache or otalgia, and it also influences the mandibular movement. Its pathogenesis is associated with trauma, weakness of the ligaments or joint capsule, abnormal chewing movements or lateral pterygoid muscles. Conservative treatment included intracapsular injection of sclerosing solutions, intramuscular botulinum toxin, intra-articular autologous blood and Prolotherapy.[20] Nagori et al. published a review of dextrose Prolotherapy in TMJ disorders. [21]They excluded animal studies, retrospective cohort studies, clinical series, case reports, review papers and uncontrolled studies. Only three randomized controlled trials (RCTs) were included in this review and presented positive results.[20,22,23] The three individual results were present below:

Kiliç et al. published a randomized clinical trial including 30 patients within two groups.[20] Participants in placebo group received 4ml normal saline + 1ml 2% articaine. In Prolotherapy group, participants received 2ml 30% dextrose + 2ml saline + 1ml 2% articaine. Outcomes were recorded till 12 months postoperatively.

Maximum inter-incisal opening (MIO) decreased significantly only in study group. Masticatory efficiency, general pain complaints and joint sounds showed improved in both groups but no significant differences. Refai et al. reported a RCT study[22] including with twelve patients with TMJ disorders. Study group with 10% dextrose showed a significant improved in maximal mouth opening (MMO) after 3 months. Both groups showed significant decrease in pain intensity but no differences between two groups. Mustafa R, et al. published another prospective RCT assessing TMJ disorder, such as subluxation or dislocation.[23] This study comprised 40 patients and randomized to 4 groups (control group, 10%, 20%, and 30% dextrose group). After one month, each group showed significant improvement in TMJ pain, MMO and joint sound, but there was no statistical differences between 4 groups. The pooling data from above three studies (Nagori et al.21) for meta-analysis revealed statistical difference in pain reduction with dextrose compared to placebo (95% CI -1.58 to -0.42) and significant difference in reduction of MMO for dextrose Prolotherapy (95% CI -5.26 to -1.28). The sample size of the meta-analysis study increased from 9-14 participants per group in individual study to 45 participants for MMO and 39 participants for TMJ pain.

Louw et al. published another randomized controlled trial in 2019 and 24 participants with TMJ disorders were randomized to two group. The study group received intra-articular injections (20% dextrose/0.2% lidocaine) for 3 monthly and followed by injections if needed through 1 year. Comparable group received with 0.2% lidocaine.[24] The outcome included Numerical Rating Scale (NRS) score for facial pain, jaw dysfunction and maximal interincisal opening (MIO, measured in millimeters). Upon the 3 month analysis, dextrose group reported decreased jaw pain (4.3 ± 2.9 points vs 1.8 ± 2.7

points), jaw dysfunction (3.5 ± 2.8 points vs 1.0 ± 2.1 points) and improved MIO (1.5 ± 4.1 mm vs -1.8 ± 5.1 mm).

Tendinopathies.

Rabago et al.[25] published a randomized controlled trial for lateral epicondylitis (tennis elbow). 26 participants randomized to dextrose group (50% dextrose 4 ml + 0.9% saline 4 ml + 1% lidocaine 2 ml), dextrose-morrhuate sodium group (5% morrhuate sodium 1ml + 50% dextrose 1.5ml + 1% lidocaine 2 ml + 0.9% saline 2.5 ml) or observation group. After 16 weeks, the dextrose groups and dextrose-morrhuate groups showed improved composite Patient-Rated Tennis Elbow Evaluation scores by a mean (SE) of 18.7 (9.6; 41.1%) and 17.5 (11.6; 53.5%) points and no adverse events reported.

Hauser et al. published a systematic review including articles from 1990 to January 2016.[26] Eighteen studies on tendinopathies were reviewed, including seven randomized control trial, ten case series and one retrospective control series. Studies for Osgood-Schlatter disease (1 RCT), temporal mandibular joint syndrome (2 RCT and 1 case series), Achilles tendinopathy (1 RCT and 3 case series), chronic groin pain (2 case series), overuse patellar tendonopathy (1 case series), plantar fasciitis (1 RCT and 1 case series), lateral epicondylitis (1 RCT and 2 case series) and chronic shoulder pain (1 RCT and 1 retrospective case controlled series) were reviewed. High concentration dextrose (from 10% to 50% dextrose) was used in each intervention group. Control group included different local anesthetic solution, exercises or normal saline in RCTs. The review showed significant improvement in pain levels and resumption of daily activities or exercise performance.

Another review article published by Rabago D in

2017 revealed similar result.[27] Six overuse tendon disorders were review, including 2 RCTs for lateral epicondylitis, 1 RCT for Osgood-Schlatter disease, 1 RCT for rotator cuff tendinopathy, 1 RCT and 1 case series for hip adductor tendinopathy, 1 review and 1 pilot study for Achilles tendinopathy, 2 review and 1 case-control study for plantar fasciopathy. These studies showed significant improvement in intervention groups using dextrose for Prolotherapy. Although Prolotherapy demonstrated a good response in above diseases, most studies were case series, while RCTs were few in each disease. The evidence is not strong, and most studies were limited by small sample size. More RCTs with higher quality are obviously necessary for stronger evidence.

Osteoarthritis(OA) and degenerative conditions.

Osteoarthritis is characterized by progressive breakdown, degradation of articular cartilage, and then disrupt collagen network that lead to joint dysfunction. Hypertonic dextrose can promote growth factors in tenocytes and fibroblasts, and positive effect to cartilage and function recovery.

Rabago et al.[28] published a randomized controlled trial with ninety patients for random injection dextrose Prolotherapy, normal saline or home exercise. Outcome is measured with the Western Ontario McMaster University Osteoarthritis Index (WOMAC) and knee pain scale after 3 months and followed by telephone at 6 and 13 months. WOMAC scores of dextrose Prolotherapy group improved more than the saline and exercise group (score change: 15.3 ± 3.5 vs 7.6 ± 3.4 vs 8.2 ± 3.3 points). Individual knee pain scores and function were also improved more. Although all injected patients experienced mild to moderate post-injection pain. There

were no other severe adverse events.

Krstičević M et al.[29] reported a review about Prolotherapy for osteoarthritis patients. Seven randomized control trials were included. Dextrose Prolotherapy were used in all intervention groups but in different doses. 10% to 25% dextrose with or without local anesthetics were used. The comparable groups included bacteriostatic water, erythropoietin, pulsed radiofrequency, hyaluronic acid and ozone-oxygen mixture. All studies showed that Prolotherapy was an effective treatment for OA. However, the evidence is limited because the trials included were low quality and only small numbers of participants were enrolled (i.e., the number of participants in each group of RCTs was less than 50 patients, from 13 to 40 participants). Although the protocols were somewhat different in each intervention group, at least 10% concentration dextrose was used for Prolotherapy and resulted in significant improvement in intervention groups. Still, RCTs with large number of participants are needed for stronger evidence of dextrose Prolotherapy in OA patients.

Another systemic review published by Arias-Vázquez et al. in 2019 showed similarly result.[30] Ten randomized clinical trials with 676 participants were included. Hypertonic dextrose was injection intra/extra-articular in all intervention groups. Although concentrations of dextrose were different in each study, at least 10% concentration dextrose was used. The result showed significant improvement in pain and physical function recovery without serious adverse reactions, and its efficacy was comparable to hyaluronic acid, ozone or radiofrequency and. Although Prolotherapy seems to be less effective than platelet rich plasma and erythropoietin in this review, hypertonic dextrose Prolotherapy is still an excellent treatment option.

Spinal and pelvic pain.

With dextrose Prolotherapy, two studies showed significantly pain improved compared with corticosteroid injection in sacroiliac(SI) joint pain group.[31-32] Besides, Hooper et al. reported interesting case series which demonstrated that Prolotherapy resulted in pain and disability improvement for chronic spinal pain patients involved in litigation.[33] However, Dagenais et al.[34] published a review study for chronic low back pain patients using five RCTs, three RCTs (206 participants) showed no differences between groups in pain or disability scores while the other two RCTs (160 participants) revealed significant differences. Those trials should not be pooled due to clinical heterogeneity. Until now, there is no study mentioning about the dose regimens or number of injections of Prolotherapy, hence we are not able to explain the dose related response.

In 2019, there is another consecutive case series proposed by Solmaz I et al.¹⁹ A total of 79 patients with failed back surgery syndrome, who had minimum of 6 months of symptoms and did not respond to 3 months of conservative methods were included in this research. 5% dextrose was injected into posterior sacroiliac ligament insertions, iliolumbar ligament insertions, transverse ligament insertions, and spinous processes. Pubofemoral ligament insertion, piriformis muscle, iliofemoral ligament insertion and ischiofemoral ligament insertion were also injected with 5% dextrose if tenderness is noted. After 1 year of follow-up, VAS score decreased from 7.9 to 2.3, and Oswestry Disability Index(ODI) decreased from 36.1 to 11.4. The author thought that lumbar, pelvic and sacroiliac ligaments are often disrupted or weakened in FBSS. Thus, dextrose Prolotherapy can improve ligaments regeneration, patient's posture, moving ability, and then improve quality of rehabilitation. Combined with dextrose

Prolotherapy and rehabilitation can effectively and efficiently decrease VAS and ODI scores.

Due to the above-mentioned controversial results, the efficacy of dextrose Prolotherapy in spinal and pelvic pain cannot be established well.

Myofascial pain syndrome.

The theoretical mechanism suggests that myofascial pain syndrome is a status of energy deficiency and depressed mitochondrial metabolism. Injection with dextrose into trigger points may stimulate energy production and then relieve symptoms. In one RCT published in 1997, injections of 5% dextrose were compared with saline solution or 0.5% lidocaine, this study revealed that dextrose group was associated with pain reduction and pressure threshold elevation.[35]

In 2020, another retrospective case series report was proposed by Yen Chou et al.[36] Forty-five patients with myofascial pain syndrome refractory to any other treatments were injected with 15% dextrose. After one month follow-up period, 80% patients reported greater than 50% improvement and 24.4% reported complete resolution of symptoms. However, the evidence is not strong enough to determine the efficacy of Prolotherapy in myofascial pain. Even more evidences are mandatory needed.

Conclusion

Dextrose Prolotherapy is an option for chronic painful musculoskeletal disorders. Dextrose Prolotherapy is a safe therapy. Few adverse events were reported and no serious complications including nerve damage, pneumothorax and infection were observed in those reviewed studies. Many of the studies cited in this review article were published long time ago; most

of them were limited with poor quality; while the intervention protocols were not uniform. More RCTs with higher quality and larger patient sample sizes are needed for further investigation. Although there is limited evidence in the efficacy for tendinopathy, chronic low back pain or myofascial pain syndrome, dextrose Prolotherapy therapy is definitely an excellent option for pain relief and function improvement associated with TMJ disorders and osteoarthritis.

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葡萄糖增生療法用於肌肉骨骼疾病之疼痛處理及其可能機轉

徐偉哲，陳士軒

骨骼肌肉疾病為慢性疼痛最常見的原因之一，這些疾病可能會嚴重地影響病人的生活品質；隨著人口老化，骨骼肌肉疾病患者數目也不斷增加。臨床上的處理可分為保守治療或是手術，如組織修補、關節置換等。隨著肌肉骨骼外科手術的費用上升，醫療系統的負擔以及群體民眾生活品質都將受影響。

葡萄糖增生療法提供一種便宜且有效的治療方式選擇。過去的報告提出透過葡萄糖增生療法可以有效改善病人臨床症狀而不需要進行手術，進而減少相關的醫療花費，然而其確切的原理目前還不完全明朗。大部分研究指出透過注射大於 10% 的葡萄糖高張溶液於肌腱韌帶處可以誘發發炎反應發生，並進一步促進注射位置的細胞增生然後修復原本受傷或脆弱的地方；另外也有研究發現使用小於 10% 的葡萄糖液，可以在不引發組織發炎的情況下直接刺激細胞和組織的增生。上述兩種機轉都可以有效的改善疼痛以及病患的生活品質。

在本篇文獻回顧中我們整理葡萄糖增生療法在各種常見的骨骼肌肉疾病的治療使用情況，他們的實證，以及可能的機轉說明。

關鍵字：葡萄糖增生療法、慢性疼痛、骨骼肌肉疾病

通訊作者：陳士軒

通訊地址：台中市南區建國北路一段 110

電話：+886 912660725

電子信箱：chen.shih.hsuan@gmail.com