Dextrose Prolotherapy for the Treatment of Chronic Shoulder Pain in Patients With Joint Hypermobility: A Case Series

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Nathan Michalak[1], Dylan Banks[2], Luke Kane[3] and Jason Siefferman[4]

[1]Department of Rehabilitation Medicine, Metropolitan Hospital, New York Medical College, New York, NY, USA. [2]Department of Rehabilitation Medicine, New York University School of Medicine, New York, NY, USA. [3]Manhattan Pain Medicine, New York, NY, USA [4]Department of Anesthesiology, Perioperative Care, and Pain Medicine, New York University School of Medicine, New York, NY, USA.

ABSTRACT: Hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSD) are common causes of chronic musculoskeletal pain. Current practices rely on analgesics, physical therapy, bracing, and assistive devices. Dextrose prolotherapy (DPT) is a regenerative injection modality used to treat chronic painful musculoskeletal conditions through stimulation of tissue proliferation. The effectiveness of DPT for the treatment of chronic shoulder pain in patients with hEDS/HSD has not been established in the literature. Three patients with hEDS or HSD presented with refractory shoulder pain due to microinstability. Patients were treated with 20% DPT injected in the glenohumeral joint and surrounding structures as indicated. Outcomes assessed were pain and clinical improvement in joint stability at 2- to 7-week follow-up intervals. All patients reported subjective improvement in their shoulder pain and function. Disabilities of the Arm, Shoulder and Hand (DASH) scores after DPT decreased from initial assessment in all patients. Patients reported a cumulative improvement in pain and joint stability with each injection. Regenerative treatment with DPT may help restore structural integrity of affected joints and serve as an adjunctive therapy for the management of chronic shoulder pain due to microinstability in patients with hEDS/HSD.

KEYWORDS: Hypermobility, Ehlers-Danlos, dextrose prolotherapy, shoulder microinstability

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CORRESPONDING AUTHOR: Jason Siefferman, Department of Anesthesiology, Perioperative Care, and Pain Medicine, New York University School of Medicine, 2 5th Ave, Suite 7, New York, NY 10011, USA. Email: jws@manhattanpainmedicine.com

Introduction

Hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSD) are a common cause of chronic musculoskeletal pain.[1] Hypermobile EDS is one of the 13 subtypes of EDS identified by the 2017 International Classification of Ehlers-Danlos Syndromes. The pathogenesis of all EDS subtypes is caused by an inherited defect in collagen structure, production, or processing. Diagnostic criteria for hEDS include a positive Beighton score with symptomatic musculoskeletal involvement and supportive skin and body system findings. No genes have been identified for hEDS, but it is inherited in an autosomal dominant pattern. Patients with symptomatic joint hypermobility who do not satisfy hEDS criteria are diagnosed with HSD. Patients with HSD may or may not have positive Beighton scores. Both hEDS and HSD result in disordered connective tissue structures and subsequent tendon laxity and reduced proprioception.[1] Joint instability results in repetitive soft-tissue trauma to ligaments and tendons, predisposing these patients to subluxation or dislocation.[2] In addition, microtrauma may cause subclinical damage that is often not supported by a recognized history of joint trauma.[2] The altered biomechanics cause compensatory changes in movement and gait that can perpetuate chronic pain.[3] Studies also demonstrate that many patients develop nerve compression and axonal neuropathies, suggesting a neuropathic component to pain.[1] Central sensitization plays a role in the chronification of pain in this patient population possibly due to continuous stimulation of peripheral nociceptors.[3]

Current management for hEDS/HSD revolves around patient education in addition to conservative treatments including analgesics, physical therapy (PT), and assistive devices. Patients with hEDS/HSD frequently report insufficient pain control even when on multiple analgesics.[4] Although patient-reported outcomes with PT are promising, patients may still suffer from chronic pain despite this intervention and experience flare-ups.[5] Inadequate pain control in this patient population is associated with psychosocial distress and poor quality of life.[1]

Prolotherapy is a practical, efficacious, and safe therapeutic option to treat musculocutaneous conditions when ligamentous laxity is the suspected pain generator.[6] The goal of prolotherapy is the stimulation of regenerative processes that restore joint stability by augmenting the tensile strength of joint stabilizing structures, such as ligaments, tendons, joint capsules, menisci, and labral tissue.[7] Hypertonic dextrose is a commonly used solution that creates local tissue trauma and generates low-grade inflammation via multiple mechanisms that in turn promote healing. The injection of dextrose induces the transport of glucose across GLUT 1-4 channels.[7] This transport, as well as the osmotic changes that occur with injection of a hyperosmolar

solution, induces pro-inflammatory cytokine release that upregulates the production of various growth factors and activates macrophages, fibroblasts, chondrocytes, and nerve cells.[6,7]

Dextrose prolotherapy (DPT) has been shown to reduce pain and disability in patients with tendinopathies of the shoulder, elbow, and ankle as well as osteoarthritis of the hand and knee.[7] Furthermore, DPT has demonstrated significant long-term improvement in pain and subluxation in patients with temporomandibular joint (TMJ) hypermobility.[8] One TMJ hypermobility study injected 50% dextrose with variable treatment duration and reported a 91% improvement in jaw dislocation or subluxations at 6 months.[8] Another meta-analysis demonstrated a significant reduction in pain secondary to chronic TMJ hypermobility after DPT.[9] However, there is limited evidence of DPT for the treatment of laxity or microinstability in other joints. A few studies have demonstrated a long-term benefit in reducing pain and improving stability in patients with anterior cruciate ligament laxity and lumbar spine ligamentous laxity.[7,10] To date, the authors found no studies that investigated the effect of prolotherapy for shoulder pain in those with hEDS/HSD. This study presents 3 cases of hEDS/HSD patients with atraumatic chronic shoulder pain with recurrent subluxations or dislocations, which responded meaningfully to DPT injections.

Case 1

A 52-year-old woman presented with bilateral shoulder and neck pain for 6 years. Her shoulder pain was persistent with an associated sense of instability and frequent subluxations despite medical management and more than 6 weeks of PT. She had no known trauma to the shoulder or neck. She reported having hypermobile joints since childhood. Her occupational history included playing guitar which required prolonged periods of end-range external rotation positioning for performances. Physical examination was notable for increased range of motion in bilateral shoulders. Provocative maneuvers were positive for O'Brien's, empty can, and multifocal instability tests bilaterally. Left shoulder ultrasound (US) examination demonstrated hypoechogenicity within the posterior labrum. A Beighton score was not calculated but based on symptomatic joint hypermobility she was diagnosed with a labral tear and shoulder microinstability secondary to HSD and overuse. Disability was assessed with the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and her score was 50.0. She underwent bilateral US-guided glenohumeral (GH) joint injections with 8 mL of 20% dextrose and lidocaine 1%. The patient was in a seated position and a 10 MHz linear probe was used to identify the posterior GH joint. The skin was prepped with chlorhexidine in a sterile fashion and a posterior injection was performed with a 22-gauge 1.5-inch needle in an in-plane approach. She experienced a diagnostic block with immediate pain resolution. She returned for follow-up appointment 2.5 weeks later and reported a lasting 75% improvement in bilateral shoulder pain along with a reduction in subluxations. Her repeat DASH score was 19.2. Repeat bilateral US-guided DPT GH joint injections were performed using the same technique and injectant. At her 5-week follow-up appointment, she reported an additional 75% improvement in shoulder pain with almost no subsequent subluxations in addition to a subjective improvement in the efficacy of PT. A DASH score completed 7 weeks after her most recent procedure was 33.3. The patient had no adverse reactions throughout her treatment.

Case 2

A 25-year-old woman presented with diffuse head, jaw, neck, and shoulder pain beginning in adolescence. Her shoulder pain was worse on the right and associated with frequent subluxations. She had no known shoulder or neck trauma. She had a history of chronic migraines, orofacial dystonia, and self-reported hypermobility. She reported inadequate relief with medical management and more than 6 weeks of shoulder PT. Physical examination was notable for increased range of motion in her bilateral shoulders with a positive apprehension test and multifocal instability. Shoulder US examination demonstrated mild bilateral joint effusions and hypoechogenicity within the infraspinatus tendon. A Beighton score was not calculated but based on symptomatic joint hypermobility she was diagnosed with shoulder microinstability and infraspinatus tendinopathy secondary to HSD. Her initial DASH score was 15.0. She underwent a right shoulder US-guided GH joint injection with 6 mL of 20% dextrose with lidocaine 1% in similar fashion to case 1. She experienced a diagnostic response with immediate relief of pain. She returned for a follow-up appointment 2 weeks later and reported 1 week of improved stability and pain in addition to a reduction in spontaneous subluxations. Dextrose prolotherapy was repeated at this visit using the same technique and injecting bilateral GH joints with 7 mL of solution each. At a follow-up visit 2 weeks later, she reported an additional 30% to 40% improvement in spontaneous subluxations as well as reduced neck pain and tension. Disabilities of the Arm, Shoulder and Hand score at this visit was 5.8. She underwent a third round of DPT with 5 mL of solution injected into bilateral GH joints as well as 3 mL into bilateral infraspinatus tendons. The patient had no adverse reactions throughout her treatment.

Case 3

A 20-year-old woman presented with several years of neck and bilateral shoulder pain with intermittent subluxations and dislocations. She had a history of hEDS diagnosed in childhood with associated migraines, Chiari malformation with craniocervical instability, cervical dystonia, mast cell activation syndrome, and postural orthostatic hypotension syndrome. She had no known history of shoulder trauma. Medical management and PT for more than 3 months did not provide adequate relief. Physical examination was notable for guarded shoulder range of motion due to pain, positive bilateral apprehension, and Neer's, Hawkins' and O'Brien's tests. Bilateral shoulder US

imaging demonstrated hypoechogenicity of the posterior labrum, subscapularis, and infraspinatus tendons with cortical changes at their attachment sites. She was diagnosed with shoulder microinstability, labral tears, and rotator cuff tendinopathy secondary to hEDS. She underwent bilateral US-guided GH joint, subscapularis, and infraspinatus tendon injections. In a seated position, the posterior GH joint was evaluated using a 10 MHz linear probe. The skin lateral to the probe was cleaned with chlorhexidine in a sterile fashion. Using a 22-gauge 1.5-inch needle, 10 mL of dextrose 20% and lidocaine 1% were injected into the joint without complication. Then, the supraspinatus and infraspinatus tendon insertion points were visualized with ultrasound, and these were similarly injected with 2 mL at each site. At her follow-up visit 2 weeks later, she reported mild improvement in discomfort and subluxations. Dextrose prolotherapy was repeated with the same technique, injecting 10 mL into each GH joint and 3 mL into each tendon. At her subsequent follow-up visit 2 weeks later, she reported additional improvement after her second injection but with some persistent shoulder pain. She deferred prolotherapy at this visit. She presented again for a follow-up visit in 4 weeks due to worsening pain and bilateral shoulder dislocations. She underwent a third DPT injection with 8 mL injected in each GH joint as well as 3 mL in the bilateral subscapularis, bilateral infraspinatus, and left supraspinatus tendons. At a 2-week follow-up, she reported an additional 30% improvement in pain and reduction in subluxation frequency.

After 4 DPT shoulder injections at 2- to 6-week intervals, the improvement in stability plateaued, and the patient reported that the therapeutic effect typically wanes over approximately 4 weeks. She went on to have 2 injections of platelet-rich plasma (PRP) using this same technique, which yielded superior results. Due to the pain and discomfort of PRP, she returns requesting DPT every few months for maintenance. She is a long-standing patient of the clinic and did not have a DASH completed prior to the initiation of injections. Her most recent DPT injection was after an 8-week hiatus, at which time she reported a DASH score of 41.6. At a follow-up visit in 6 weeks, the patient's DASH score was 19.2. The patient had no adverse reactions throughout her treatment.

Discussion

The established cornerstone of pain management in patients with hEDS/HSD is PT.[5] While PT can strengthen stabilizing musculature, address posture and gait abnormalities, and improve proprioception, it cannot sufficiently address the underlying hypermobility due to ligamentous laxity.[3]

The patients in this case series exhausted multiple modalities of treatment for chronic shoulder pain associated with hypermobility. In these cases, PT and oral medications provided inadequate pain relief and functional stability. This study used DPT injections for their shoulders with the specific goal of targeting supporting structures and improving joint stability through proliferation of tissues. These patients reported improved pain and a decreased number of subluxations in between interval follow-up visits. They also reported improvement in their disability as evidenced by the decrease in their DASH scores.

Prolotherapy stimulates the proliferation of collagen by initiating a healing cascade and may shorten or strengthen a lax ligament, or promote healing of a torn tendon. The final phase of repair involves replacing type 3 collagen with type 1 collagen. Dextrose concentrations greater than 10% are considered proinflammatory and have been shown to stimulate fibroblast proliferation, tendon hypertrophy, and ligament size. In both animal and tendon models, DPT augments the tensile strength of connective tissue, such as ligaments, tendons, joint capsules, menisci, and labral tissue.[6] This can help stabilize the joint capsule and surrounding structures and restore a joint's intrinsic stability.[7] Due to the nature of ligamentous laxity in these individuals, the authors suspect that multiple injections, performed in a series of 2 to 4 weeks apart, are required to initiate proliferation and subsequently maintain momentum in its regenerative effect until adequate tensile strength is reached. The authors used a 20% dextrose injectant as it is suspected to have a maximal inflammatory effect to promote ligamentous constriction without inducing neurolysis.[6] As noted in the first case, the patient's DASH score increased 7 weeks after her most recent injection. Repeat injections may be required to help combat the forces of routine use and prevent the return of microinstability. It is conceivable that, in patients with more severe disease such as in our third case, this may not be an achievable goal and that the benefits will plateau. This raises the question of utility for other modalities, such as PRP, that may have different regenerative mechanisms to complement the mechanism of DPT. The authors note that the third case did not have a DASH score completed prior to the initiation injections. However, the authors believe that after the 8-week hiatus of injections, the patient returned to a state of microinstability and the DASH score completed at that time represents a close baseline. Investigators may find that, within the heterogeneous population of hEDS/HSD, certain phenotypes or even certain patterns of injury respond better to one regenerative modality than another.

As a case series, this report lacks numbers and consistency in methodology for outcome measurement. To date, the authors found no other published cases of hEDS/HSD shoulder instability or microinstability treated with DPT or other regenerative modalities. As this study found benefit with this minimally invasive and cost-effective treatment, the authors felt it prudent to share. Future large-scale studies will hopefully elucidate a clear protocol for each regenerative modality for treatment of multiple joints.

Conclusion

As demonstrated in this case series, patients with hEDS/HSD may benefit from DPT as an adjuvant treatment for chronic shoulder pain when microinstability is present. Further studies are needed to investigate the full therapeutic benefit of DPT in

patients with hEDS/HSD and to create a more standardized approach to this modality.

Ethics approval and consent to participate

Ethics approval is not applicable. The authors obtained written informed consent from the patients for the inclusion of their medical and treatment history within this work.

Consent for publication

The authors obtained written informed consent from the patients for publication of this work.

Author contributions

Drs Michalak, Banks, Kane, and Siefferman contributed to the conception of the work, interpretation of data, manuscript preparation and review, final version approval, and agreement to be accountable for all aspects of the work.

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Availability of data and materials

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ORCID iD

Nathan Michalak https://orcid.org/0000-0001-9227-6984

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