Prolotherapy for Musculoskeletal Pain and Disability in Low- and Middle-Income Countries

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KEYWORDS

• Prolotherapy • Osteoarthritis • Tendinopathy • Chronic pain
• Low- and middle-income countries • Regenerative therapy

KEY POINTS

- Chronic musculoskeletal pain and disability reduce the quality and quantity of life worldwide, with a disproportionately high impact in low- and middle-income countries.
- Traditional, complementary, and integrative medicine may have much to offer in the prevention and treatment of chronic musculoskeletal pain and disability.
- Prolotherapy is an injection-based complementary therapy that addresses causes of pain and disability at the tissue level, supported by high-quality evidence for osteoarthritis, tendinopathy, and low back pain.
- Prolotherapy is a straightforward office-based procedure that relies on common, inexpensive materials, and does not require refrigeration, making it an attractive treatment option in low- and middle-income countries.
- Although not typically part of conventional medical training, not-for-profit organizations are teaching clinicians and treating patients with prolotherapy in low- and middle-income countries through service-learning projects.

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GLOBAL IMPACT OF BACK PAIN, OSTEOARTHRITIS, AND TENDINOPATHY

Musculoskeletal (MSK) health problems are major contributors to the global burden of disease as assessed by the metric "years lived with disease" (YLD). They cause 21.3% of the total burden as measured by YLD, second only to mental and behavioral problems,[1,2] and are a worldwide threat to healthy aging. Some MSK conditions cause disproportionate impact; low back pain (LBP) is the leading specific cause of YLD-defined disability, "other MSK disorders," which include heterogeneous conditions including chronic tendon- and ligament-related pain, ranked sixth, and hip and knee osteoarthritis (OA), ranked 11th.[3,4]

Low- and middle-income countries, where MSK conditions are the third greatest threat and cause of death and disability, experience a disproportionate burden.[1,2] Characteristics predisposing to MSK problems and common in higher-income countries include an aging demographic and increasing obesity. Associations resulting in disproportionate MSK burden in low- and middle-income countries include rapid population growth, the high-intensity physical nature of much subsistence work, and the general poor access to health promotion and treatment services.[5]

Government and aid organizations have historically focused less on MSK and more on life-threatening conditions, such as communicable diseases, and building the overall health care capacity. Content experts have called for more attention, indeed a "paradigm shift," among global agencies to address the large and growing burden of disability caused by MSK conditions. They have suggested large-scale policy change and local efforts at the level of international health agencies, such as the World Health Organization (WHO) and national health agencies, and have advocated for the use of core principles of local ownership, local decision-making, community and stakeholder engagement, integration of services into the larger policy and structures, and avoidance of current unimodal approaches. Particularly relevant to this report is the call for collaboration with international organizations and local stakeholders in the pursuit of community-based treatment efforts.[5]

Although such calls to action are clear and evidence based, they may ignore a group of potential impactful therapies that have not gained a broad recognition. Often missing from discussions about treatment of MSK conditions on a global scale is the category of traditional, complementary, and integrative medicine (TCIM). October 2018 marked the 40th anniversary of the WHO Alma Ata Declaration, a document which established health as a human right and placed the development of primary health care at the center of global health priorities.[6] It also identified TCIM as having a place in health care systems. Primary care "relies, at local and referral levels, on health workers, including physicians, nurses, midwives, auxiliaries, and community workers as applicable, as well as traditional practitioners as needed, suitably trained socially and technically to work as a health team and to respond to the expressed health needs of the community."[6] This declaration was among the first major policy statements to both acknowledge TCIM in primary care and suggest its potential to make a positive impact on health.

WHO defines TCIM medicine as a "broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health system."[7] Numerous well-known, evidence-based TCIM therapies, including meditation, acupuncture, yoga, tai chi, massage, and other movement and body techniques, as well as prolotherapy, may offer solutions to some MSK chronic pain and disability in low- and middle-income countries.

PROLOTHERAPY

Definition and History

Prolotherapy is an emerging injection-based TCIM therapy for chronic MSK conditions used by both primary care and MSK specialty clinicians.[8] Less well-known than some TCIM MSK therapies, prolotherapy was developed in the United States in the early and middle twentieth century, and remains largely outside conventional medicine. Prolotherapy is most often taught using peer learning, and in conference, workshop, and formal continuing medical education settings. However, the evidence base supporting prolotherapy is growing, and includes effectiveness and efficacy studies for treatment of high-burden conditions of OA and LBP, and in ligament and tendon disorders owing to overuse. Prolotherapy is unique in its capacity to deliver active therapy to a variety of local tissue and pain generators, both within and around joint spaces in a single treatment session. Treatment materials are inexpensive and require no cold chain; the injection protocols, although operator dependent, are straightforward to learn using palpation guidance.[9–11] Prolotherapy may therefore have application to the growing burden of MSK pain and disability in low- and middle-income countries. In this article, we define prolotherapy, provide an review of evidence, and describe the efforts of 2 nonprofit organizations to introduce prolotherapy to low- and middle-income countries through humanitarian service-learning projects.

Developed in the early twentieth century, the first peer-reviewed report about prolotherapy appeared in 1937.[12] George Hackett, MD, a general surgeon in the United States, later formalized injection techniques based on clinical experience and research. Believing tissue proliferation to be an essential aspect of the effects of the injections, he named the procedure: "To the treatment of proliferating new cells, I have applied the name prolotherapy."[13] Because the purported effects of prolotherapy include revitalization and reorganization of degenerative tissue, it has also been categorized by some content experts as a "regenerative" injection therapy.[14] Practitioners have refined the injection protocols using consensus-based efforts to provide guidelines and clinical practice.[9]

Treatment commonly consists of several injection sessions conducted every 4 to 8 weeks over several months. Hypertonic dextrose is the most commonly used injectant. During a treatment session, dextrose is injected at sites of tender ligament and tendon attachments, and also in adjacent joint spaces.[15] It is hypothesized that the solutions that are injected cause local irritation, with subsequent inflammation and anabolic tissue healing, which improves joint stability, biomechanics, function, and, ultimately, decreases pain.

Mechanism of Action

A tissue-level pain-control mechanism is hypothesized but has not been well elucidated; however, it is likely multifactorial, involving effects at multiple tissue types and planes, and associated with both the physical injection procedure and the biological effects of the injectant. Mechanistic studies of dextrose prolotherapy suggest a noninflammatory proliferant effect,[16–18] potential clinical effects via brief stimulation of the inflammatory cascade,[19] chondrogenesis,[20] and a clinical analgesic effect with or without hypertonic levels of dextrose.[21,22]

Conditions for Which Prolotherapy Is Evidence Based

The first systematic review of prolotherapy for all indications for MSK found 42 published reports from 1937 to 2005.[8] Thirty-six were case reports or case series and reported positive findings for patients with a wide variety of chronic, painful MSK

conditions refractory to then-current best care; the strength of methodology varied among these studies. Most of the participants assessed were treated for LBP; other conditions included knee and finger OA, shoulder dislocation, neck strain, costochondritis, lateral epicondylosis, and fibromyalgia. These pragmatic studies assessed prolotherapy in clinical settings and provided the platform from which to perform more formal studies. Prolotherapy has primarily been subjected to a descriptive review inclusive of all randomized clinical trials and included 15 such studies. The rate of publication of high-quality clinical trials is accelerating.[23] Here, we review the major studies most relevant for 3 sets of conditions, OA, tendinopathy, and LBP, which are of particular relevance to low- and middle-income countries.

Osteoarthritis

Of all indications for which prolotherapy is used, clinical trial data best support its use for OA. Early studies by Reeves and Hassanein[24,25] assessing intra-articular dextrose injections for knee and finger OA reported efficacy compared with control injections, and suggested the need for more rigorous study. Two groups conducted more rigorous trials of prolotherapy for knee OA. Using the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC) (0–100-point scale), they documented improvement after prolotherapy of more than 12 points, which is the minimal clinically important difference on the WOMAC scale for knee OA.[26,27]

Rabago and colleagues[15] conducted an open-label pilot study of prolotherapy and established methodological elements, effect size, and overall feasibility for a randomized controlled trial (RCT). Participants reported 15.9 points of improvement on the overall WOMAC scores. Shortly thereafter, Dumais and colleagues[28] corroborated these findings in a crossover study in which participants who received physical therapy and prolotherapy were compared with patients receiving physical therapy alone. At 16 weeks, prolotherapy was added to the physical therapy group; and the change on the aggregate WOMAC scale attributed to prolotherapy alone was 11.9 points.

Using injection protocols from their pilot study, Rabago and colleagues[21] compared prolotherapy with at-home exercise and blinded saline injection in a 3-arm RCT. Prolotherapy participants reported statistically and clinically relevant score improvement compared with both control groups at 9, 24, and 52 weeks, culminating in a 15.3-point improvement on the WOMAC assessment: nearly twice that of the controls. These are the most robust data favoring prolotherapy, and suggest that prolotherapy, performed by a trained operator, results in safe, substantial, and sustained improvement on knee-specific quality of life indicators. Three systematic reviews, 2 with meta-analyses, found that prolotherapy resulted in significant, clinically important improvement for knee OA without adverse events concurred with these findings.[29–31] A subsequent open-label study followed participants to an average of 2.5 years postenrollment and reported continued improvement to an average of 20.9 points on the WOMAC scale.[32] Of these participants, 82% improved compared with their baseline status; however, 18% worsened, consistent with the natural history of knee OA. No study has identified baseline predictive markers of success with prolotherapy.

Tendinopathies

There is also evidence that prolotherapy is successful in several chronic, painful conditions caused by tendon overuse. The purported mechanism of prolotherapy is well matched to the current understanding of tendinopathy caused by tendon overuse, because it is primarily a noninflammatory, degenerative condition. We provide a description of selected studies for tendinopathies of particular relevance to low- and middle-income countries: lateral epicondylosis (LE), Achilles tendon, and rotator

cuff tendinopathies. Other MSK conditions not reviewed here, but which are also supported by high-quality data, include hip adductor and patellar tendinopathy, plantar fasciopathy, and temporomandibular joint dysfunction.[33,34]

Lateral epicondylosis or tennis elbow Two pilot-level RCTs suggest that prolotherapy is efficacious for LE. In a 2-arm study comparing prolotherapy with blinded saline injections, Scarpone and colleagues[35] assessed 20 adults (10 per group) with severe LE refractory to standard care and who were considering surgery. Participants who were treated with prolotherapy reported, on a 0 to 10 point visual analog scale (VAS), significantly decreased scores over 16 weeks of 4.6 points, whereas controls reported decreased scores of 1.0 point. Participants who received prolotherapy also showed significantly improved isometric strength compared with controls, and improved grip strength compared with baseline status. These clinical improvements in prolotherapy subjects were maintained at 52 weeks. These data were corroborated by Rabago and colleagues[36] in a pilot study using the Patient-rated Tennis Elbow Evaluation, a validated measure of primary outcome. Both studies suggest efficacy but are limited by small sample size. Data from both studies were used to establish methods for an ongoing, more definitive study.[37]

Achilles tendinopathy Maxwell and colleagues[38] conducted a case series (N = 36) to assess whether prolotherapy, injected under ultrasound guidance, decreases pain and changes ultrasound-based parameters of tendon character. At 52 weeks, participants reported improvement in VAS-assessed pain severity by 88%, 84%, and 78% during rest, "usual" activity, and sport, respectively. Tendon thickness decreased significantly; however, other ultrasound-based criteria were not correlated with self-reported outcomes. Prolotherapy has been assessed in a high-quality RCT comparing prolotherapy, physiotherapy, and combined care. Participants reported earlier response, and the study reported improved cost-effectiveness, when physiotherapy and prolotherapy were combined, compared with either treatment alone.[39]

Rotator cuff tendinopathy Bertrand and colleagues[40] assessed use of prolotherapy for rotator cuff tendinopathy in a 3-arm blinded RCT. Patients received prolotherapy, blinded injection, or superficial blinded injections at 0, 1, and 2 months. The primary outcome was improvement in shoulder pain greater than or equal to 2.8 points on 0 to 10 using the VAS. The percentage of participants receiving prolotherapy meeting this criterion was statistically greater than in the controls who received the superficial lidocaine injection (59% vs 27%), but not in the group who received the lidocaine injection (59% vs 37%). These findings suggest that the study may have been under powered or that the deep lidocaine injections had a treatment effect above that of placebo. The findings were incorporated into a systematic review and compared with several different injection therapies for symptomatic rotator cuff syndrome. Network meta-analysis showed that prolotherapy was superior to other injection therapies in pain reduction at long-term follow-up.[41]

Chronic low back pain

Four RCTs have assessed prolotherapy for nonsurgical nonspecific LBP; 3 used phenol-glycerine-glucose (P2G) as the injectant[42–44]; the fourth and most rigorous trial used dextrose.[45] Each RCT used a protocol involving injections to the ligamentous attachments of the L4-S1 spinous processes, sacrum, and ilium. Although many outcome measures varied across the studies, the percentage of participants reporting over 50% improvement in pain and disability scores at 6 months was a common assessment.

In the methodologically strongest RCT, participants were randomized to 1 of 4 groups: dextrose and physical therapy, dextrose and "normal activity," saline injections and physical therapy, or saline injections and normal activity.[45] At 12 months, participants in all groups reported reduced pain (by 26%–44%) and disability (by 30%–44%) scores; the percentage of participants who reached at least a 50% pain reduction ranged from 36% and 46% across the groups. Change in outcome scores favored the dextrose groups, but not by statistically significant margins. Most (55%) reported that improvement in pain and disability had been worth the effort of undergoing the study interventions. Whereas the study was reported as negative, subtler interpretation is reasonable. Two factors likely served to limit detection of a therapeutic effect favoring the active arm. First, sham injection procedures contain several therapeutic components, including needle stick, pressure/volume tissue-level changes, and acute injury from needle stick on bone with initiation of blood-based irritation and inflammatory healing cascade.[46] Each would minimize the difference between control and active injection groups. Second, the study was likely under powered given the use of such an active control.

Direct sensorineural effects of dextrose are suggested by the results of a novel RCT assessing dextrose administered as an epidural injection. Maniquis-Smigel and colleagues[22] compared serial blinded 5% dextrose injections with saline injectant in 35 participants with chronic LBP and buttock or leg pain. A statistically significant analgesic effect was seen in those who received dextrose in comparison with those who received normal saline injections, which lasted from 15 minutes to 48 hours ($P<.05$); this effect endured with repeated injection in a longer-term follow-up study.[47] The speed of analgesia onset after an epidural injection suggests a potential direct effect of dextrose at the level of peripheral nerves.

Interpretation of LBP prolotherapy trials is challenging; methodological questions have been raised.[48] A systematic review[49] found insufficient evidence to recommend prolotherapy for nonspecific LBP; however, while early clinical trial data offer generally promising results, more rigorous, sufficiently powered trials are needed. Studies assessing prolotherapy in patients with more narrowly focused diagnoses of LBP have been done in an effort to determine the underlying pathology most responsive to prolotherapy. Cusi and colleagues[50] assessed 25 participants with sacroiliac joint dysfunction refractory to 6 months or more of physical therapy, and noted improvements in pain and disability scores at follow-up after 26 months. Khan and colleagues[51] assessed 37 adults with coccydynia refractory to other care, and also noted a reduction in pain scores from 8.5 to 2.5 points at 2 months. Miller and colleagues[52] assessed prolotherapy as an intradiscal injection for leg pain in participants who had an imaging-confirmed moderate-to-severe degenerative disc disease, and who had not responded to either physical therapy or 2 fluoroscopically guided epidural corticosteroid injections. After an average of 3.5 sessions of biweekly, fluoroscopically guided intradiscal injections with 25% dextrose, 43% showed a significant, sustained treatment response. Although these studies of prolotherapy for focused causes of LBP were uncontrolled, they suggest the effectiveness and the need for further research to assess the use of prolotherapy for specific causes of LBP.

Contraindications/Side Effects and Adverse Events

Prolotherapy seems safe when practiced by a trained clinician. Injections should be performed using universal precautions. Contraindications, side effects, and adverse events have been reviewed.[23] There are few absolute contraindications to prolotherapy, and include skin or joint infection, rheumatological flare, allergy to injectant, and

treatment with immunosuppressive medications. Relative contraindications include gouty arthritis flare, acute fracture, bleeding disorders, and use of anticoagulants. After prolotherapy treatment, patients may report acute injection-related discomfort and tissue "fullness." Pain occurs in approximately 10% of patients within the first 72 hours postinjection.[21] Additional injection-related procedural risks include lightheadedness, allergic reaction, infection, or nerve injury.

PROLOTHERAPY AND SERVICE-LEARNING ORGANIZATIONS

Although prolotherapy is not generally taught in conventional medical education centers, organizations with a focus on so-called regenerative injection therapies offer conference and workshop instruction, and limited training worldwide (**Table 1**). At least 2 of these organizations also do service-learning work, with some projects in low- and middle-income countries; these include the American Association of Orthopaedic Medicine (AAOM) and the Hackett Hemwall Patterson Foundation (HHPF). Their work exemplifies a means of dissemination of the teaching and practice of prolotherapy, while delivering care to underserved populations.[53,54] Each of these organizations has developed a curriculum, teaching style, and practice standards, which include didactic and workshop training in conference settings in the United States and intensive, hands-on clinical practice experiences in low- and middle-income countries; the HHPF has developed a formal set of procedural guidelines to structure these experiences.[9]

The AAOM was founded in 1983 by physicians from the United States and Canada to advance nonsurgical Orthopaedic medicine. The roots of the HHPF extend to 1969, when founders established an annual service trip to Honduras to provide prolotherapy to the underserved. While both organizations have grown to include other activities, each provides prolotherapy for chronic MSK pain through their service-learning work. The organizations and their service-learning trips share several characteristics. Each organization is a 501c3 not-for-profit entity and conducts medically oriented trips in Latin America that integrate service and learning. Each organization conducts hands-on prolotherapy training as part of a larger service project. Licensed physicians enroll in the fee-based experience, which is eligible for continuing medical education credit in the United States. The learning experience includes on-site lectures and demonstration, and mentored hands-on experience in clinics established for the project that provide free care to local patients. Both groups also train local clinicians in prolotherapy at no cost. Locations include 3 cities in Honduras (La Ceiba, Tela, and Olanchito), 2 in Mexico (Guadalajara and Cancun), and 1 in Peru (Lima). Both groups work with other regional centers. Local partners vary and include community groups, churches, the Honduran Red Cross, local physician groups, and university departments (see **Table 1**). At each site, representatives of AAOM or HHPF work with local partners to establish temporary clinics, inform patients of care options provided free of charge or at nominal cost, obtain consent for prolotherapy care, complete relevant history and examination, and obtain basic demographic information. Patients are treated on a first-come, first-served basis; local interpreters are available on-site to enable a real-time communication between the patients and the treating clinicians. Patients are examined to establish whether prolotherapy is appropriate for them; if so, prolotherapy is explained, and interested patients complete an informed consent for the procedure. Patients are treated using standards of medical professionalism, hygiene, and procedural safety that mirror those of the United States. Existing prolotherapy teaching materials are used; the HHPF also uses standardized teaching materials for procedural approaches to each joint/area that have been developed using a

Table 1
Characteristics of prolotherapy service-learning trips of 2 North American medical organizations

Organization	Clinic Location	Inception Date	Local Partner Organization	Duration of Service-Learning Project (wk)	Average Number of Patients Undergoing Prolotherapy	Number of Visiting Trainees	Number of Local Trainees
HHPF	La Ceiba, Honduras	1969	Cruz Roja Hondureña (Red Cross)	2	650	4–7	1–2
	Tela, Honduras	1988	Sala Evangelica Church	2	600	4–7	1–2
	Olanchito, Honduras	2004	Community leader and Sociedad de Agricultores y Ganaderos de Olanchito (SAGO)	2	550	4–7	1–2
	Guadalajara, Mexico	2006	Palabra de Vida Church and local physician	1	575	17–18	2–3
AAOM	Cancun, Mexico	2007	Local mayor, community government, and local Department of Family Medicine	1	600	12–16	6
	Lima, Peru	2011	Clinica Internacional del Peru, local PM&R clinics, and local physician	1	450	8–12	6
	Guadalajara, Mexico	2013	Universidad de Guadalajara, Hospital Civil de Guadalajara, and local physician	1	600	12–16	6

Abbreviations: AAOM, American Association of Orthopaedic Medicine; HHPF, Hackett Hemwall Patterson Foundation; PM&R, physical medicine and rehabilitation.

Table 2
Medical organizations providing didactic and hands-on prolotherapy instruction

Australia	
Australian Association of Musculoskeletal Medicine	https://aamm.org.au/courses-conference/
Asia	
Hong Kong Institute of Musculoskeletal Medicine	http://www.hkimm.hk/
Taiwan Association of Prolotherapy and Regenerative Medicine	http://www.taprm.org/
Europe	
European School of Prolotherapy	proloterapia.it/en/
North America	
American Association of Orthopaedic Medicine	aaomed.org/
The American Osteopathic Association of Prolotherapy Regenerative Medicine	prolotherapycollege.org/
Canadian Association of Orthopaedic Medicine	Caom.ca
Hackett Hemwall Patterson Foundation	hhpfoundation.org/
South America	
Latin American Association of Orthopaedic Medicine	www.laomed.org

All URLs accessed March 18, 2019; the table presents a sample of prolotherapy learning opportunities worldwide.

consensus model by organization members who are experts in prolotherapy techniques.[9]

The service-learning projects offered by both groups have a successful track record of patient care safety and, anecdotally, positive impact on health; each organization safely treats over 1000 patients annually and trains dozens of physicians. Anecdotally, patients express satisfaction with care; many return each year for treatment of the same or other MSK conditions. Side effects and adverse events are rare and do not seem to exceed those in developed countries. In addition to these 2 leading organizations, other medical groups have formed. On occasion, students and teachers from these 2 "parent" organizations have gone on to found their own teaching groups; one can now learn prolotherapy worldwide (**Table 2**). Such growth suggests an increasing interest among clinicians and patients in prolotherapy, and points the way to efforts that can scale up this care worldwide. A short-term goal common to all such organizations is to build in mechanisms to systematically assess project-specific patient and community outcomes to better understand the effect of such efforts. Longer-term efforts should include improved local community and other stakeholder involvement, and integration of training efforts into formal medical education and policy considerations.

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