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Current Concepts of Prolotherapy in Orthopedic Surgery

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Abstract

Context: Prolotherapy is a popular injection-based complementary treatment, which has shown promising results in the treatment of sprained and degenerated ligaments, and damaged dense connective tissues' structures. More research was conducted in this area and many authors declared successful results for different indications.

Evidence Acquisition: The purpose of this study was to present a literature review regarding the current concepts of prolotherapy injections and improvements in the orthopedic clinical care practice. The Medline and PubMed databases were searched for the articles related to prolotherapy injections in the field of orthopedic surgery and additionally the reference list of each article was also included to provide a comprehensive evaluation.

Results: Numerous studies have been conducted on prolotherapy injections for different indications for orthopedics clinical care practice. Prolotherapy injections have successfully used for major orthopedic procedures in terms of rotator cuff lesions, knee ligamentous lesions, osteoarthritis-cartilage defects, and ligament-tendon injuries. Most of the studies showed that prolotherapy provided faster and better healing of tissues.

Conclusions: There is a great interest to prolotherapy in orthopedic clinics, especially to manage musculoskeletal lesions. More research conducted in this area and many authors declared successful results in their studies. In spite of this increasing trend for prolotherapy injections, there were only one or two clinical studies investigated prolotherapy injections for different indications and most of them have limited participants, short-term follow-up or poor quality studies. There is still need for further high-quality studies investigated optimal strategy of the injections of prolotherapy.

Keywords: Prolotherapy Injections, Preparation Protocols of Prolotherapy, Current Indications of Prolotherapy

1. Context

Musculoskeletal injuries are very common, and one of the global health problems. Numerous research have been conducted into this area; however, there is still controversy about the most effective method (1-3).

In recently prolotherapy has successfully used in the treatment of sprained and degenerated ligaments, damaged dense connective tissues structures including tendons and enthesis, chondromalacia patella and osteoarthritis (4-10). Too many advantages exist with this method; including easy application, shortening the rehabilitation process and cost effectiveness. It also provides healing of the structures (ligaments and tendons) then; stability and functionality of the tissues are restored (11).

Prolotherapy injections are prepared with distinct concentrations of hypertonic dextrose. The solutions are injected to specific regions of the effected body part, and then provide the osmotic rupture of local cells (12). This leads to an increase of glucose in the extracellular matrix, which increases growth factors and causes deposition of new collagen into different types of human cells and subsequent healing (13-16).

2. Evidence Acquisition

The aim of this study was to present a systemic review regarding the most recent progress in prolotherapy injections and current indications in orthopedic clinical care practice. The Medline and PubMed databases (1946 to the 30th of May 2016) were searched for the articles related with prolotherapy in the field of orthopedic surgery and additionally the reference list of each article was also included to provide a comprehensive evaluation.

2.1. Inclusion Criteria

In this study, English-language clinical studies (case reports, case series, randomized and nonrandomized clinical studies) related with prolotherapy methods in orthopedic surgery were included. Every form of prolotherapy components (e.g., dextrose or sodium morrhuate) was included, and there was no limitation in preparing the process of prolotherapy. Because of the lack of relevant, matching studies, there was no limitation in comparators.

2.2. Exclusion Criteria

Studies evaluating different treatment methods other than prolotherapy injections, prolotherapy procedures nonrelated with the orthopedic surgery, and nonclinical study types (e.g., systemic reviews, meta-analysis, animal studies, and cadaver studies) were excluded from the study.

The search results accounted for 135 articles. Sixty-three articles were excluded from the study because of nonrelevant topics, thus 72 articles were included in the study. Thirty articles were clinical studies, 3 articles were animal studies, and 39 articles were reviews and other study types. The article selection process was shown in Figure 1.

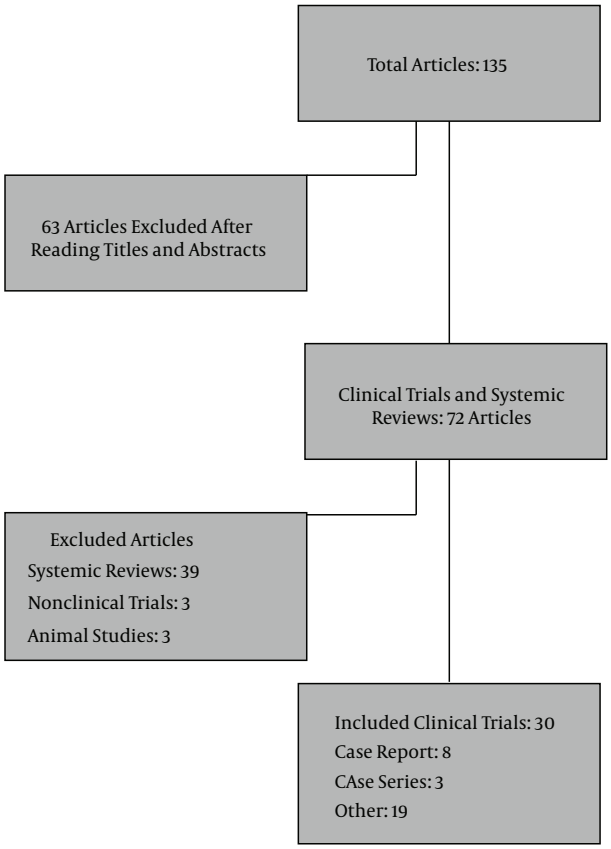

Figure 1. Article Selection Process

3. Results

3.1. Preparation Protocols of Prolotherapy

There is no standard protocol for preparation of prolotherapy solutions. Different concentrations and combinations of prolotherapy solutions used in the literature for different indications. Concentration of dextrose differs from five to twenty-five percent and the optimal concentration remains obscure (17, 18). Jensen K et al. (19, 20) stated that dextrose solutions below the concentration of 10% stimulate proliferation of cells and tissue but do not have a significant effect on histological inflammatory reaction with these concentrations. When dextrose is injected in greater than the concentration of 10%, osmotic (concentrated) gradient stimulates accumulation of growth factors and inflammatory cells that initiates the wound-healing cascade. Therefore, the concentrations of dextrose greater than 10% should be preferred for proliferation and histological inflammatory reaction.

In combination with dextrose, different concentrations of lidocaine, sensorcaine and xylocaine were the most used pharmaceutical agents (20-22). There was no animal or clinical study in the literature that compared the effectiveness of different concentrations or combinations of prolotherapy solutions (12, 19). Therefore, there is a need for further studies investigated optimal strategy of the injections of prolotherapy.

3.1.1. Number and Interval of Injection Sessions

The number and interval of injection sessions are also different in the studies; some authors preferred single, others preferred serial sessions, therefore number and interval of injection sessions depend on experience and local practice patterns. Prolotherapy is an invasive treatment method and repeated injection sessions seem to be excessive and costly. In the previous studies that investigated efficacy of prolotherapy in the treatment of various musculosketal conditions, at least three injection sessions were performed. Moreover, some of the studies declared that most effective benefits could be gained with repeated injections (13, 23-27).

3.1.2. Injection Procedures

Prolotherapy injections can be performed with palpation or ultrasound-guided. Chen et al. (28) compared ultrasound-guided and palpation guided injection in the treatment of plantar fasciitis and stated that therapeutic outcomes were significantly better with ultrasound-guided injection than palpation-guided injection. They also stated that effectiveness and duration might increase with the precise injections into the target points. They also observed higher rates of recurrence with palpation-guided injections (29). Because of the anti-inflammatory effects, NSAIDs counteract the pro-inflammatory mechanism; therefore, all NSAIDs should be stopped 2 - 3 weeks prior to a prolotherapy procedure and then no NSAIDs are used for the duration of treatment with prolotherapy.

There is no consensus regarding the volume of prolotherapy solutions. In the previous studies, 2 cc to 4 cc of prolotherapy injected to every painful points (6, 8, 9, 13).

3.2. Main Indications of Prolotherapy in Orthopedic Surgery

3.2.1. Knee Osteoarthritis

Knee osteoarthritis (OA) is a chronic joint disease; characterized by knee pain, stiffness, and functional impairment. Many studies are available about efficiency about prolotherapy injections in the treatment of osteoarthritis. Most of these studies have shown beneficial effects of prolotherapy injections in terms of improvement in pain scales (between 36% to 55% improvement) and WOMAC subscales (30-33). Injection sites varies according to studies; some authors were performed combined intra-articular and extra-articular injection for bony attachments of LCL or other ligaments, some preferred single intra-articular injection. The first seemed to be more promising method for patients with ligament injury in the younger ages, and also elderly patients with knee OA and have extra-articular degenerated ligaments. Mechanic instability commonly occurs in patients with osteoarthritis due to injury or degeneration of knee ligaments. The studies evaluated prolotherapy injections to the osteoarthritic patients with traumatic knee instability have shown beneficial outcomes in terms of decreasing pain and healing knee ligaments that provide mechanic stability of knee joint. In these studies favorable results of prolotherapy have shown in terms of improvements of cartilage defects and healing of extra-articular injured ligaments (22, 34). Rabago et al. (43 investigated long-term outcomes (mean of 2.5 years) of prolotherapy in the patients with mild-to-severe knee OA in an open-label follow-up study. Prolotherapy injections were resulted significant improvements in terms of knee functions, pain intensity, and stiffness. Its effect has been shown to be better than saline injections and pulsed radiofrequency in the randomized and controlled studies (30, 35). No significant difference was found between prolozone and prolotherapy in a randomized clinical trial (9). Also, 12.5% to 20% of dextrose concentrations were used in the studies and success rates were similar, thus 12.5 of dextrose may be used for osteoarthritis (8, 9, 22, 30-36). As prolotherapy is a simple, rapid, and safe option, it can be considered a first-line conservative therapy for knee OA.

3.2.2. Chondromalacia Patella

Chondromalacia patella is one of the most common diseases of knee accompanied by chronic pain and dysfunction. The disease is defined as the degeneration, and thinning of the cartilage of the patella. The disease affects both younger and older patients and if it is not properly treated, it could be induced disruption of cartilage and eventually resultant osteoarthritis (37). In spite of recent treatment modalities including anti-inflammatory drugs, exercise, physical therapy, and corticosteroid injections, there is a need for new methods in some group patients. Hauser et al. (10) investigated the efficiency of prolotherapy in 61 patients with chondromalacia patella in their retrospective study. They faced successful results with prolotherapy injections in terms of enhancing the knee functions and pain relief. Despite the aforementioned studies, there is a need for prospective, randomized or controlled trials in this area.

3.2.3. Epicondylitis

Epicondylitis is a common cause of elbow pain in the middle ages. It is usually associated with repetitive and forceful activity believed to be a degenerative process, which stems from repetitive microtrauma (13). Prolotherapy is thought to be promising in this area; however, a few available studies declared contradictory results. Scarpone et al. (13) used prolotherapy injections in the treatment of chronic lateral epicondylitis with comparison of placebo of saline injections in a double-blind randomized controlled trial. In the prolotherapy group, pain intensity and grip strength were significantly improved up to a mean follow-up of 50 weeks. Then Carayannopoulos et al. (38) used prolotherapy injections with the comparison of corticosteroid injections in the treatment of lateral epicondylitis in another randomized controlled trial. They observed significant improvement at 3 or 6 months at both of the groups, and there was no significant difference between the groups. There is a still need for more randomized controlled studies have larger participants and have more objectively outcome measures. Most of the studies were conducted with lateral epicondylitis, therefore the efficiency of prolotherapy is not known yet.

3.2.4. Rotator Cuff Lesions

Rotator cuff lesions are very common in all age groups (39). A considerable number of patients can be healed with conservative methods; however, these may not be efficient in some group of patients, thus there is a need for new methods in these patients (40-42). Prolotherapy injections was firstly used by Lee et al. (43) in the nonrandomized retrospective case-control study. They observed that prolotherapy injections provide improvement in pain, disability, isometric strength, and shoulder motion in patients with refractory chronic rotator cuff disease resistant to conservative treatment. Then, Bertrand et al. (44) used prolotherapy in the treatment of rotator cuff tendinopathy in a randomized and controlled study with a control group,

which were subjected of saline injections, and observed pain improvement and patient satisfaction, but there was no significant difference in the shoulder pathological healing when compared to the control group.

3.2.5. Plantar Fasciitis

Plantar fasciitis is a major cause of foot disability in the ages of 40 and 60 years (45, 46). Conservative treatment modalities are not effective in approximately 10% of the patients and there is a still need for more effective treatment modalities for this group of patients (47). There is limited evidence about prolotherapy in the treatment of plantar fasciitis. In the available literature, prolotherapy was only used by M B Ryan (48) in the treatment of chronic plantar fasciitis of 20 patients and found a significant decrease in VAS scores when compared to preoperative values, and they also determined good to excellent results in 16 of 20 patients (80%). There is a need for randomized controlled trials, which have a larger number of participants in the area. Kim et al. comprised prolotherapy and platelet rich plasma in the treatment of chronic recalcitrant plantar fasciitis in a single-blinded, randomized, controlled study, and concluded that platelet rich plasma may lead to a better initial improvement in function, however all the two methods were effective and there was no significant difference between the groups (33).

3.2.6. Knee Collateral Ligaments

Collateral ligaments provide medial and lateral stability of the knee joint. They usually injured from direct trauma with varus and valgus stress (49). There is very limited evidence about prolotherapy in the treatment of collateral ligaments. In the literature there is only a case report accessed that gives evidence about prolotherapy injections in the treatment of MCL lesion of male rugby player sustained valgus stress to his knee (50). After 12 weeks of first prolotherapy injection he had no residual symptoms or functional deficit. Patient was evaluated with MRI sixth months after trauma and the MRI findings showed a well-healed, relatively homogeneous MCL and also subchondral bone marrow edema at the corner of the lateral tibial plateau had also diminished.

3.2.7. Osteoarthritis of Carpometacarpal or Metatarsal Joints

The symptomatic osteoarthritic hand is common over the ages of 70 and has been estimated as 13.4% for men and 26.2% for women (51). Corticosteroid injection is the most common method and showed benefits in the short- time period; however, its effectiveness was stated to be temporary by many authors in the long-term (52). Azadeh Jahangiri et al. (53) investigated prolotherapy in the treatment of osteoarthritis of the first carpometacarpal joint in a randomized clinical trial with comparison of corticosteroid injections. In the short-time (1 month), they showed that corticosteroid injections had better outcomes than prolotherapy. However, partial symptoms in the corticosteroid group were recurred in the long period (6 months) and the prolotherapy group had significantly better outcomes than the corticosteroid group in terms of functions and pain after 6 months of first treatment.

3.3. Complications

Prolotherapy is known to be safe method when compared to other injection based complementary methods. The studies reported very few complications including allergic reactions, superficial tissue infections and nerve damage (12). There is no risk for tendon rupture injecting in and around a tendinopathic tendon, this may occur when the tendon insertion is too weakened. It is presumed to be effective by stimulating weakened structures such as ligaments and tendons to strengthen, tighten and heal by the induced proliferation of cells (54, 55).

3.4. Limitations

Only two databases (The Medline and PubMed library) were searched for articles; it was seemed that only the positive findings of prolotherapy were presented and counterpoint articles were neglected in this review. However, most of the included articles had positive findings about prolotherapy injections. There may be some counterpoint articles in the non-English literature or the other articles indexed in other databases, leading selection bias. Screening references of identified case series and trials may result in an over representation of positive studies in this review, because trials with a positive result are more likely to be referred to in other publications, leading to reference bias.

3.5. Conclusions

In recently, there is a great interest to prolotherapy in sports medicine and orthopedic clinics, especially to manage chronic musculoskeletal system disorders. More research conducted in this area and many authors declared successful results. In the clinical practice its effectiveness was firstly showed in the painful overuse tendinopathies, by the time, it was used for osteoarthritis and successful clinical outcomes were obtained especially in the long-periods. In spite of new development knowledge about prolotherapy injections, there were only one or two clinical studies investigated prolotherapy injections for different indications and most of them have limited participants, short-term follow-up or poor quality studies. There is still need for further high-quality studies investigated optimal strategy of the injections of prolotherapy.

Footnote

Authors' Contribution: All authors contributed to and approved the manuscript.

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Table 1. Characteristics of Included Studies

Site	Ref.	Outcome Measure	Mean Follow-up	Comparator	Study Type	Main Results
Knee osteoarthritis	Reeves et al. (2000)	Pain, range of motion, radiographic measures of joint narrowing and osteophytosis, measurement of anterior displacement	1 year	Saline	Randomized prospective double-blind placebo-controlled study	Prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis. When ACL laxity is present in these osteoarthritic patients, it is also improved.
	Rabago et al. (2012)	Osteoarthritis index, pain	1 year		Single-arm uncontrolled study	Prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores.
	Solmaz et al. (2013)	Osteoarthritis index, pain, radiologic evaluation	1 year		Case Report	Significant improvement was noted at osteoarthritis index, stiffness, and physical function. The osteoarthritis level of the patient was also improved at radiological evaluation after a year.
	Rabago et al. (2013)	Osteoarthritis index, pain, post-procedure opioid medication use, and participant satisfaction	1 year	Saline, home exercises	Randomized controlled study	Prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises.
	Rabago et al. (2013)	Osteoarthritis index, pain, stiffness, function, and magnetic resonance imaging	1 year	Saline, home exercises	Two-arm, partially blinded, controlled trial	Prolotherapy resulted in safe, substantial improvement in knee osteoarthritis-specific quality of life compared with control over 52 weeks.
	Robago et al. (2014)	Osteoarthritis index, pain	1 year		Prospective three-arm uncontrolled study	Prolotherapy using dextrose and morrhuate sodium injections for participants with mild-to-severe osteoarthritis resulted in safe, significant, sustained improvement of knee pain, function, and stiffness scores compared to baseline status.
	Rahimzadeh et al. (2014)	Pain, satisfaction	12 week	Prolotherapy wih erythropoietin, pulsed radiofrequency	Double-blind randomized clinical trial	Intra-articular prolotherapy with erythropoietin was more effective in terms of pain level reduction and ROM improvement compared with dextrose and pulsed radiofrequency.
	Hashemi et al. (2015)	Osteoarthritis index, pain	3 months	Prolozone (Intraarticular Ozone)	Randomized controlled study	Pain intensity and functional scores significantly decreased and increased, respectively. However, there was no significant difference between the two groups (prolozone and prolotherapy).
	Robago et al. (2015)	Osteoarthritis index	2.5 years		Postclinical-trial, open-label follow-up study.	Prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years.
	Eslamian et al. (2015)	Pain, range of motion, and osteoarthritis index	24 weeks		Single-arm prospective study	Significant improvement of validated pain, ROM, and WOMAC-based function scores in the patients with osteoarthritis, when baseline levels were compared at 24 weeks.
	Topol et al. (2016)	Visual cartilage growth assessment, Osteoarthritis index	7.75 months		Case Series	Compared with baseline status, functional scores were improved. Biopsy specimens showed metabolically active cartilage with variable cellular organization, fiber parallelism, and cartilage typing patterns consistent with fibro- and hyaline-like cartilage.
Chondromalacia Patella	Hauser et al. (2014)	Pain, range of motion, stiffness, and crepitus	14.7 months		Retrospective study	Statistically significant decreases were determined in pain at rest and exercise. Stiffness and crepitus decreased after prolotherapy, and range of motion increased.

Lateral Epicondylitis	Scarpone et al. (2008)	Pain, extension and grip strength	1 year	Prolotherapy with sodium morrhuate, Saline	Double- blind randomized controlled trial	Prolotherapy with dextrose and sodium morrhuate was well-tolerated, effectively decreased elbow pain, and improved strength testing in subjects with refractory lateral epicondylitis compared to control group injections.
	Carayannopoulos et al. (2011)	Pain, disability, physical function	6 months	Corticosteroid injection	Randomized controlled trial	There was no significant difference between the prolotherapy and corticosteroid groups regarding change in pain and functional scores.
	Robago et al. (2013)	Physical function, pain-free grip strength and magnetic resonance imaging	32 weeks	Prolotherapy with dextrose-morrhuate sodium solution, Wait and see	Single- blind, pilot-level, randomized controlled trial	Prolotherapy resulted in safe, significant improvement of elbow pain and function compared with baseline status and follow-up data and the wait-and-see control group.
Rotator Cuff Lesions	Lee et al. (2015)	Pain, disability, physical function, range of motion	1 year	Physical therapy	Retrospective case control study	Compared with the control group, the VAS score, SPADI score, isometric strength of shoulder abductor, and shoulder AROM of flexion, abduction, and external rotation showed significant improvement in the prolotherapy group.
	Bertrand et al. (2016)	Pain, ultrasound examination	9 months	Enthesis-Saline Superficial-Saline	Randomized and controlled study	Prolotherapy resulted in superior long-term pain improvement and patient satisfaction compared with blinded saline injection over painful entheses, with intermediate results for entheses injection with saline.
	Seven et al. (2016)	Pain, disability, physical function	1 year		Case report	Pain, disability and functional scores were significantly improved.
Plantar Fasciitis	Ryan et.al. (2009)	Pain at rest, activities of daily living, and after physical activity	11.8 months		Case series	Prolotherapy showed a good clinical response in patients with chronic plantar fasciitis in so far as pain was reduced during rest and activity.
	Kim et al. (2013)	Pain, physical function	6 months	Platelet rich plasma	A single-blinded, randomized, controlled study	Each treatment seems to be effective for chronic recalcitrant plantar fasciitis, expanding the treatment options for patients in whom conservative care has failed. The PRP treatment also may lead to a better initial improvement in function compared with prolotherapy.
Knee Collateral Ligaments	Ada et al. (2015)	Pain, range of motion	8 weeks	-	Case report	?
Osteoarthritis of carpal, carpometacarpal or metatarsal joints	Jahangiri et al. (2014)	Pain, physical function and strength	6 months	Corticosteroid	Double-blind randomized clinical trial	For the long-term, prolotherapy seems to be more advantageous, while the two treatments were comparable in the short-term.
	Reeves et. al. (2000)	Pain at rest, joint movement and grip, and range of motion	6 months	Saline	Prospective randomized double-blind placebo-controlled trial	Pain at rest and with grip improved more in the dextrose group but not significantly. Improvement in pain with movement of fingers improved significantly more in the dextrose group. Flexion range of motion improved more in the dextrose group.
Anterior cruciate ligament injury	Reeves et al. (2003)	Pain, range of motion, measurement of anterior displacement	36 months	Saline	Prospective consecutive patient trial	Prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis.
	Grote et al. (2009)	anterior drawer test and MRI	15 weeks	None	Case report	By 15 weeks, the patient had no instability climbing and descending stairs, the anterior drawer test was negative and MRI showed an intact ACL with fibrosis. Subsequently, she returned to full sport activity.
Metatarsophalangeal Joint Instability	Ojofeitimi et al. (2016)	Physical functionality, health survey	6 month	None	Case report	Functional scores and patient health survey was improved. One year after discharge, the dancer reported pain-free dancing with no taping or padding.

Achilles tendinosis	Yelland et al. (2011)	Functional scores pain, stiffness and limitation of activity scores	12 months	Eccentric loading exercises (ELE), Eccentric loading exercises combined with prolotherapy	A single-blinded randomized clinical trial	Prolotherapy and particularly eccentric loading exercises combined with prolotherapy give more rapid improvements in symptoms than eccentric loading exercises alone but long-term VISA-A scores are similar.
Sternoclavicular subluxation	Stein et al. (2011)	Range of motion, physical functionality	20 months		Case report	Prolotherapy is a completely safe and effective fashion, and allows the patient to resume full lifestyle activities without restriction.
Ischiofemoral Impingement Syndrome.	Kim et al. (2014)	Pain, magnetic resonance imaging	6 months		Case report	Pain severity score using the visual analog scale was remarkably decreased and magnetic resonance imaging revealed a slightly decreased enhancement of the quadratus femoris muscle compared with that on previous images.
Coccygodynia	Khan et al. (2008)	Pain	3 months		Case series	Dextrose prolotherapy is an effective treatment option in patients with chronic, recalcitrant coccygodynia and should be used before undergoing coccygectomy.