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 affected 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 methods in 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](image-url)

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 musculoskeletal 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.
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 six 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 a 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.

References

<table>
<thead>
<tr>
<th>Site</th>
<th>Ref.</th>
<th>Outcome Measure</th>
<th>Mean Follow-up</th>
<th>Comparator</th>
<th>Study Type</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee osteoarthritis</td>
<td>Reeves et al. (2000)</td>
<td>Pain, range of motion, radiographic measure of joint narrowing and osteophytosis, measurement of anterior displacement</td>
<td>1 year</td>
<td>Saline</td>
<td>Randomized prospective double-blind placebo-controlled study</td>
<td>Prolotherapy injection with saline resulted in statistically significant improvement in knee osteoarthritis. When ACL laxity is present in these osteoarthritic patients, it is also improved.</td>
</tr>
<tr>
<td></td>
<td>Rabago et al. (2012)</td>
<td>Osteoarthritis index, pain</td>
<td>1 year</td>
<td>Single-arm uncontrolled study</td>
<td>Prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solmaz et al. (2013)</td>
<td>Osteoarthritis index, radiologic evaluation</td>
<td>1 year</td>
<td>Case Report</td>
<td>Prolotherapy resulted in safe, substantial improvement in knee osteoarthritis-specific quality of life compared with blinded saline injections and at-home exercise.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabago et al. (2013)</td>
<td>Osteoarthritis index, pain, stiffness, function, and magnetic resonance imaging</td>
<td>1 year</td>
<td>Two-arm, partially blinded, controlled trial</td>
<td>Prolotherapy resulted in clinically meaningful and sustained improvement of pain, function, and stiffness scores compared to baseline status.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hauser et al. (2005)</td>
<td>Osteoarthritis index, pain</td>
<td>2 months</td>
<td>Prolotherapy with etoposide, pulsed radiofrequency</td>
<td>Pain intensity and functional scores significantly decreased, respectively; however, there was no significant difference between the two groups (prolotherapy and placebo).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabago et al. (2015)</td>
<td>Osteoarthritis index</td>
<td>2.5 years</td>
<td>Post-clinical trial, open-label follow-up study</td>
<td>Prolotherapy resulted in significant, progressive improvement of knee pain, function, and stiffness scores among most participants through a mean follow-up of 2.5 years.</td>
<td></td>
</tr>
<tr>
<td>Chondromalacia Patellae</td>
<td>Hasegawa et al. (2016)</td>
<td>Pain, range of motion, osteoarthritis index</td>
<td>24 weeks</td>
<td>Single-arm prospective study</td>
<td>Significant improvement of validated pain, ROM, and WOMAC functional scores among the patients with osteoarthritis, whose baseline levels were compared at 24 weeks.</td>
<td></td>
</tr>
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</table>

**Table 1. Characteristics of Included Studies**
### Lateral Epicondylitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Time</th>
<th>Intervention</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarpone et al. (2008)</td>
<td>Pain, extension and grip strength</td>
<td>1 year</td>
<td>Prolotherapy with sodium morrhuate, Saline</td>
<td>Double-blind randomized controlled trial</td>
</tr>
<tr>
<td>Bahr et al. (2018)</td>
<td>Physical function, pain-free grip strength and magnetic resonance imaging</td>
<td>12 weeks</td>
<td>Prolotherapy with fluorouracil and sodium morrhuate solution, Wait and see</td>
<td>Single-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Lee et al. (2005)</td>
<td>Pain, disability, physical function, range of motion</td>
<td>1 year</td>
<td>Physical therapy</td>
<td>Retrospective case-control study</td>
</tr>
<tr>
<td>Bertrand et al. (2006)</td>
<td>Pain, ultrasound examination</td>
<td>9 months</td>
<td>Bicortical Saline, Superficial Saline</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Seveno et al. (2005)</td>
<td>Pain, disability, physical function</td>
<td>1 year</td>
<td>Case report</td>
<td>Pain, disability and function scores were significantly improved.</td>
</tr>
</tbody>
</table>

### Plantar Fasciitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Time</th>
<th>Intervention</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan et al. (2009)</td>
<td>Pain at rest, activities of daily living, and after physical activity</td>
<td>11.8 months</td>
<td>Prolotherapy</td>
<td>Case series</td>
</tr>
<tr>
<td>Kim et al. (2003)</td>
<td>Pain, physical function</td>
<td>6 months</td>
<td>Placebo rich plasma</td>
<td>A single-blinded, randomized controlled study</td>
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</table>

### Knee Collateral Ligaments

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Time</th>
<th>Intervention</th>
<th>Trial Design</th>
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<tbody>
<tr>
<td>Johangst et al. (2016)</td>
<td>Pain, range of motion</td>
<td>8 weeks</td>
<td>-</td>
<td>Case report</td>
</tr>
<tr>
<td>Reeves et al. (2009)</td>
<td>Pain at rest, joint movement and grip, and range of motion</td>
<td>6 months</td>
<td>Saline</td>
<td>Prospective randomized double-blind placebo-controlled trial</td>
</tr>
<tr>
<td>Reeves et al. (2000)</td>
<td>Pain, range of motion, measurement of anterior displacement</td>
<td>15 months</td>
<td>Saline</td>
<td>Prospective randomized patient trial</td>
</tr>
</tbody>
</table>

### Anterior Cruciate Ligament Injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Time</th>
<th>Intervention</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gore et al. (2009)</td>
<td>Anterior drawer test and MRI</td>
<td>15 weeks</td>
<td>None</td>
<td>Case report</td>
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### Metatarsophalangeal Joint Instability

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Time</th>
<th>Intervention</th>
<th>Trial Design</th>
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</thead>
<tbody>
<tr>
<td>Opejot et al. (2016)</td>
<td>Physical functionality, health survey</td>
<td>6 month</td>
<td>None</td>
<td>Case report</td>
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<tr>
<td>Condition</td>
<td>Authors (Year)</td>
<td>Primary Outcomes/Methods</td>
<td>Follow-up</td>
<td>Study Design</td>
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<tr>
<td>Achilles tendinosis</td>
<td>Yelland et al. (2011)</td>
<td>Functional scores, pain, stiffness and limitation of activity</td>
<td>12 months</td>
<td>Single-blinded randomized clinical trial</td>
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<td>Sternoclavicular subluxation</td>
<td>Stein et al. (2011)</td>
<td>Range of motion, physical function</td>
<td>20 months</td>
<td>Case report</td>
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<tr>
<td>Ischiofemoral impingement syndrome</td>
<td>Kim et al. (2014)</td>
<td>Pain, magnetic resonance imaging</td>
<td>6 months</td>
<td>Case report</td>
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<td>Coccygodynia</td>
<td>Khan et al. (2008)</td>
<td>Pain</td>
<td>3 months</td>
<td>Case series</td>
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