Chapter

Features and Clinical Effectiveness of the Regenerative Injection Treatments: Prolotherapy and Platelet-Rich Plasma for Musculoskeletal Pain Management

Ilker Solmaz and Aydan Orscelik

Abstract

Pain is a symptom caused by a disease process and/or tissue injury. With the prolongation of life expectancy in humans, the incidence of degenerative joint diseases and as a result pain has increased. Unfortunately, a method of treatment that stops or reverses progression by affecting the pathogenesis in these diseases has not been developed. Physical therapeutics such as medicine and physical rehabilitation often are prescribed for patients suffering with pain. Recently, in addition to these routine therapies used in pain treatment, many regenerative injection-based therapies, including prolotherapy (PrT) or platelet-rich plasma (PRP) have been widely used. PrT is using for damaged or degenerated connective tissue healing, such as ligaments, tendons, and cartilage. The combination of local inflammatory effect, stimulation of local growth factor release, and down regulation of neuropathic inflammation can be defined as the mechanism. As a result of these, joint instability and ligament laxity reduce and pain decrease. PRP is the cellular component of the plasma. Although PRP is used for the same reasons as PrT, it can be used in acute cases unlike PrT. This chapter is intended to understand the use of regenerative injection therapies (PrT and PRP) better in the treatment of pain.

Keywords: regenerative injection treatments, prolotherapy, platelet-rich plasma, musculoskeletal pain

1. Introduction

New developments are taking place every day in every field of medicine. Disease prevention, early diagnosis, and the definite treatment method call has become the target of scientists. With the prolongation of life expectancy in humans, the incidence of degenerative joint diseases and as a result pain has increased. Unfortunately, a method of treatment that stops or reverses progression by affecting the pathogenesis in these diseases has not been developed.

Pain is a symptom caused by a disease process and/or tissue injury. Physical therapeutics, such as medicine and physical rehabilitation, often are prescribed for

patients suffering with pain [1]. Recently, in addition to these routine therapies used in pain treatment, many regenerative injection based-therapies, including prolotherapy (PrT) or platelet-rich plasma (PRP) have been widely used. The evidence for these treatments has arisen from the basic sciences and has been transformed into clinical research through controlled researches [2].

2. Regenerative injection treatments

2.1 Prolotherapy

PrT is derived from the words "proliferation" and "therapy" in Latin [3]. In the 1930s, it was introduced in the USA first, but the word "Prolotherapy" was first used by George Hackett in 1950. Dr. Hemwall's studies reported that 82% of the patients provided pain remission [4]. George Hackett formed the injection protocols for PrT in the 1950s depending on his clinical experience [4, 5]. Death of a case has been reported due to an allergic reaction due to phenol injection during PrT in 1959. After this negativity, this method has been removed to history [6].

PrT is an increasingly popular regenerative injection-based therapy and using for damaged or degenerated connective tissue healing, such as ligaments, tendons, and cartilage [7–10]. Following injury, chronic musculoskeletal pain develops if connective tissue repair is insufficient [4, 5]. Chronic musculoskeletal pain and disability often result from degeneration associated with these structures. PrT treatment can help us to correct this degeneration at the tissue level [4, 9]. We can correct this degeneration at the tissue level with the help of PrT. Pain reduction and regeneration mechanism are not clearly understood yet [7, 8]. However, the combination of local inflammatory effect, stimulation of local growth factor release, and down regulation of neuropathic inflammation can be defined as the mechanism [8, 11]. As a result of these, both joint instabilities with ligament laxity may reduce and also pain may reduce [12].

The proliferant solutions are used for injection into tender ligamentous and tendinous attachments and adjacent joint spaces. Irritants, osmotics, and chemotactics are proliferants commonly used in PrT. Irritants are phenol, guaiacol, and tannic acid. These damage cells. Particulates, that is, pumice flour, are also irritants but make cellular trauma and attract macrophages directly. Sodium morrhuate is a chemotactic and attract inflammatory cells. Glucose, glycerin, and zinc sulphate are the osmotic proliferants and cause osmotic shock to cells [12]. The most common injectant used in the randomized controlled trials (RCTs) is hypertonic dextrose [7, 11, 13]. Proliferant solutions may cause osmotic rupture of cells in the area in which they are applied and may direct to growth factor increase in various cells of human. Also, a hypertonic environment may lead to the release of DNA-encoding growth factors [11, 14]. Furthermore, various proliferant solutions cause fibroblast stimulation. Growth factors activate and also release the fibroblasts. The active fibroblasts secrete new collagen fibrils. Collagen fibrils are essential for the repair of damaged ligament and tendons and support healing [4, 10]. PrT tighten and strengthen the ligaments, tendons, and joint stabilizing structures. So, PrT could improve the stability of the joints [4, 10, 12, 15]. Increased joint stabilization could be associated with tissue healing process by increasing local blood flow and the excitability of mechanoreceptors and also by decreasing the excitability of pain receptors [4].

Instead of phenol, hypertonic dextrose solution can be done safely for PrT nowadays. The risk of side effects and complications is very low. As a result of this, hypertonic dextrose solutions with different concentrations (10–30%) have been

commonly used in studies and books to date for PrT treatments. In these studies, greater than 10% of dextrose solutions proposed to use inflammatory response and proliferation. An animal study is designed for determining the optimal concentrations of dextrose solutions. This claimed that under the concentration of 10% only induce cell proliferation; however, do not have any effectivity on inflammation histology [16]. However, 5% dextrose solution increased gene expression in angiogenetic factors (platelet-derived growth factor (PDGF)-A and B, insulin-like growth factor-I, and vascular endothelial growth factor-A) and in apoptotic factors (caspase-3 and -8) in adult fibroblast culture [17]. High concentrations of glucose stimulate the PDGF activation. PDGF has two effects; first, it induces TGF-beta gene expression in mesangial cells, and second, it stimulates DNA synthesis [18]. Above the glucose concentrations of 10% make stimulus for the connective tissue growth factor and other genes expression in mesangial cells [19]. Cartilage volume stability improved by PrT injections, and this can be evaluated by magnetic resonance imaging [16].

Excessive pain and fatigue due to inflammatory reaction can occur after the PrT injections. According to this rarely, treatment can be abandoned. To reduce the pain, hypertonic dextrose commonly combined with lidocaine, sensorcaine, and xylocaine as local anesthetics [20]. The local anesthetics delay and disrupt wound healing by inhibiting collagen synthesis in fibroblast tissue [21]. However, this condition disrupts the outcome of the treatment.

2.1.1 Classification

PrT can be classified as enthesofascial, myofascial, and neurofascial according to injection location.

2.1.1.1 Enthesofascial/intra-articular PrT

Enthesofascial/intra-articular PrT is the classic and traditional method of PrT. The injection location is on to the bony cortex/enthesis where the ligaments attach to or into joints.

2.1.1.2 Myofascial PrT

Myofascial PrT is the other type of PrT. In this type, injection location is soft tissue of the bony cortex and below the subcutaneous fascia. This is used for degeneration of muscle and tendon, tears of muscle, defects of fascia. It prevents function of muscle, or fascia surrounded by neovessels or neonerves.

2.1.1.3 The neurofascial PrT

The neurofascial PrT is another type for PrT. Injection location is near to the peripheral sensory nerves and particularly their fascial penetrations. So this is performed to subcutaneous tissue. The goal of PrT is repairment or functional restoration of soft tissue, and neurofascial PrT produces the restoration of full function in small nerves. The reparative proteins and their correlation with nerve repairment are less well known. Nerves and ligament and tendon are covering with mainly collagen-based structure (i.e., perineurium). Nerves must take place in repair of soft tissue faults and that rather probably are planned to behave a similar order of growth factors. According to these reasons, dextrose is potentially therapeutic to small nerves [3]. However, this classification of neurofacial PrT is not widely accepted.

2.1.2 Indications and contraindications of PrT

Indications of PrT are chronic musculoskeletal disorders such as chronic low back pain, osteoarthritis, epicondylitis, and rotator cuff lesions.

Contraindications of PrT are hereditary or acquired bleeding tendency, osteomyelitis, systemic infection, chronic infection history or active infection in the treatment region, rheumatic or other systemic inflammatory disease, oncological diseases, having been injected local corticosteroid within 12 weeks and allergy to the solution that is using for PrT.

2.1.3 Disorders for PrT

2.1.3.1 Chronic low back pain

Chronic low back pain is a common disease in the population. It causes temporary or permanent disability [12]. The results of the studies on this subject contain contradictions. Intra-articular PrT injection is significantly superior to corticosteroid injection in sacroiliac joint pain [22]. A RCT of sclerosing injections reported that PrT has similar result as saline plus lignocaine in chronic low back pain [23]. Injections performed once a week for 3 weeks unlike to normal use. Another RCT for nonspecific chronic low back pain compared PrT injections, saline injections, and exercises. All ligament injections caused meaningful decreases in pain and disability along the follow-up. Results are similar for PrT and saline or for exercises and daily life [24]. When integrated to spinal manipulation, exercise, and other interventions, PrT may have better impact on chronic low back pain and disability [12]. Also vitamin B12 usage increases the effectiveness of the treatment [25].

2.1.3.2 Osteoarthritis

Knee osteoarthritis is an important disease with increasing rate of pain, functional disability, and stiffness. A systematic review and meta-analysis compare the effect of dextrose PrT against control injections and exercise in the treatment of osteoarthritis. Dextrose PrT is superior to exercise, local anesthetics, and corticosteroids in 6 month follow-up [26]. Similar to this, a 3-arm, blinded, RCT compared dextrose PrT, saline, and at-home exercise, and PrT is better clinical enhance of pain, function, and stiffness than saline injections and at-home exercises [27]. There are more studies showing the success of PrT in knee osteoarthritis. Injection locations are different according to researchers; a combination of extra and intra-articular injection [28, 29], and only intra-articular [30, 31]. Combination of injections is thought to be an important treatment in young people with connective tissue disorders and also in elderly patients with severe knee osteoarthritis alternative to knee prosthesis. In these studies, it is reported that it not only reduced the pain but also corrected knee mechanical instability and cartilage damage.

Corticosteroid injections are an important treatment modality in symptomatic hand osteoarthritis [32]. The short-term effectiveness is well but the long-term effect is temporary. In carpometacarpal joint osteoarthritis, corticosteroid injection is superior to PrT at 1 month follow-up. Symptoms repeated with corticosteroid injection at the end of the sixth month, but improvement continued with PrT in the long-term and recurrence was less. PrT had better results in long term than corticosteroid injections [33].

2.1.3.3 Epicondylitis

Although PrT is a promising method for the treatment of epicondylitis, there are contradictions in a limited number of studies. In a randomized double-blind study PrT and placebo injections in patients with lateral epicondylitis compared PrT and placebo injections in patients with lateral epicondylitis. PrT was found to be significantly successful in pain and function [13]. A three-arm RCT reported PrT with dextrose and PrT with dextrose and sodium morrhuate were similar successful results for pain and function than wait and see group [7]. Subsequently, a double blinded RCT compared PrT and the corticosteroid injections, and no difference was found between groups in the same indication.

2.1.3.4 Rotator cuff injuries

PrT injection to the shoulder region was first reported by Lee et al., and successful results have shown in patients with resistant to conservative treatment [34]. Similar results were obtained in RCT's [14, 35].

2.1.4 Adverse events

Adverse events change according to the localization of injections. Pain and stiffness may increase temporary, and these are the most common events. Also post-injection headache, postmenopausal spotting, pain with neurological features, nausea, and diarrhea may occur, but transiently [12].

2.2 Platelet-rich plasma

PRP is the cellular component of the plasma. It has a higher platelet concentration than whole blood [36]. Platelets are obtained by fragmentation of precursor megakaryocytes [37]. Activated platelets release clotting and growth factors in the α-granules. The main growth factors secreted by α-granules of platelets and effective in wound healing are known as PDGF, IGF-1, VEGF, TGF-β, and b-FGF [38]. Other factors such as serotonin, adenosine, dopamine, calcium, histamine, ADP, ATP, and catecholamine in the dens granules of platelets also play a role in tissue regeneration [39].

Growth factors assure the release of other growth factors, enhancing healing process in chronic injuries and quickening repair in acute lesions [38–40]. It was first used to accelerate the wound healing of cutaneous ulcers in the 1980s [41]. The potential of regeneration and curative effect of PRP in oral implantology has been demonstrated [42]. The usage of PRP has spread to other clinics [43].

Cellular components of plasma consist of 93% erythrocytes, 6% platelet, and 1% leukocytes. PRP contains platelets 3–5 times higher than whole blood. Depending on this, it contains growth factors in hyperphysiological rate [36].

There is no accepted clear platelet concentration value for PRP. However, there are studies that report the healing effect when the number of platelets up to 150,000/μl, and 350,000/μl in whole blood is above 1,000,000/μl in 5 ml plasma [42].

PRP is provided by centrifugation of autologous anticoagulant whole blood. Prior to centrifugation, citrate is added to whole blood for bounding ionized calcium and coagulation is prevented. After centrifugation, whole blood is divided into three layers according to gravity. The top layer consists of plasma, the middle layer called as "buffy coat" consists of platelets and leukocytes, and the lowest layer consists of erythrocytes [43]. A second centrifuge is applied to the buffy coat and plasma section, indicating that PRP and platelet poor plasma may lead to further separation [44, 45].

According to preparation technique and the resulting product ingredients, PRP is classified as: pure-PRP (P-PRP), leukocyte and leucocyte and PRP (L-PRP), and pure platelet-rich fibrin (P-PRF), leucocyte and platelet-rich fibrin (L-PRF). Nowadays, leukocytes can increase local inflammation, and leucocyte-poor content is shown to be superior to rich content. Centrifugation and activation methods are two important determinants of PRP quality and growth factor release. To date, there is no worldwide accepted PRP preparation protocol [45].

2.2.1 Indications and contraindications of PRP

Indications of PRP can be summarized as the acute/chronic musculoskeletal, cartilage and bone diseases such as chronic tendinopathies and enthesitis, acute/chronic ligament injuries, acute/chronic muscle tears and strains, osteoarthritis, osteochondritis dissecans, arthroplasty operations, meniscus injuries, delayed fracture healing, nonunions, intervertebral disc injuries.

PRP's being an autologous graft minimizes the risk of allergic reaction and infectious disease. The side effects are pain formation due to local inflammatory response at the injection site, scar formation, and calcifications as infection and further possibilities at the rate of risk at all injections. Patient selection should be performed carefully as there is a risk of serious allergic reaction to bowel thrombin. The contraindications of PRP are the presence of tumors and metastatic disease, active infection, thrombocytopenia, anemia, pregnancy and lactation, and bowel thrombin allergy [46].

Acetaminophen and narcotic analgesics can be administered against pain, while nonsteroidal anti-inflammatory drugs are often banned for 2–4 weeks. It is thought that nonsteroidal anti-inflammatory drugs can inhibit the prostaglandin pathway and the beneficial effects of growth factors. Furthermore, in patients who received systemic steroids or immunosuppressive drugs, steroid injections were used instead of lesions in the last 6 weeks, and PRP injections were not preferred for NSAIDs in the last 7–10 days [36].

2.2.2 Disorders for PRP

2.2.2.1 Rotator cuff injuries

The recovery process in massive chronic rotator cuff tears often results with failure. PRP injection is not more effective than saline [47]. During the arthroscopic repair of full-thickness rotator cuff tears, PRP induces reduction in the pain level at the early postoperative period, a significant increase in shoulder function tests, and shoulder external rotation muscle strength in the short term; but there is no significant difference in pain, function, and MRI results in the long-term [48]. While PRP usage did not create a difference in arthroscopic repair of full-thickness rotator cuff tears, PRP was better for improvement in the arthroscopic repair of small and medium rotator cuff tears [49].

2.2.2.2 Lateral epicondylitis

The common feature of the lateral epicondylitis studies is the standardization of patient selection. PRP treatment is performed by the patients with chronic lateral epicondylitis who did not benefit from conservative treatment. Therefore, unlike to other disorders, standardization of the patient selection seems to be provided in the lateral epicondylitis.

PRP is superior to steroid injections for reducing pain and improving function [50–52]. Steroid injections have better results in the first weeks, deterioration occurs

especially after 26 weeks [50], and at the end of the second year, patients return to the baseline level [51]. PRP has a progressive improvement effect [50, 51], and this effect continues in the long term [51].

In two studies conducted by the same author applying the same diagnosis and treatment, the total number of patients can be considered as 350. PRP by using the peppering technique is applied to extensor carpi radialis brevis tendon and vicinity. Success of PRP was found more than 80% after 6 months of treatment [53].

Repeated injections are not superior to single dose administration in the treatment of chronic lateral epicondylitis [54].

2.2.2.3 Patellar and Achilles tendinopathy

PRP provides healing in pain and function even in patients with resistant patellar tendinopathy. Unlike the other injuries, 5 ml of PRP is injected into the tendon three times with an interval of 15 days [55, 56]. Even, ultrasound-guided PRP (by using peppering technique and ~2 ml/2 times/2 weeks intervals) was found to be superior from ESWT in the treatment of patellar tendinopathy [57].

While PRP treatment was shown to be significant in patellar and Achilles tendinopathy case series, it was similar as saline injection in RCTs. However, it is indicated that saline injection cannot be considered as placebo because of the mechanical effect caused by the needle and bleeding [58].

PRP injections were considered successful in the treatment of chronic refractory Achilles tendinitis [59–61].

2.2.2.4 Osteoarthritis

Intra-articular PRP and hyaluronic acid provide similar clinical improvement. The success rate was higher in the joints with low degeneration at 6 and 12 month

Figure 1.
Intra-articular PRP applications to the knee joint.

Application	Indications	Contraindications
PrT	Chronic musculoskeletal disorders; Chronic low back pain, Osteoarthritis, Epicondylitis, Rotator cuff lesions.	Hereditary or acquired bleeding tendency, Osteomyelitis, Systemic infection, Chronic infection history or active infection in the treatment region, Rheumatic or other systemic inflammatory disease, Oncological diseases, Having been injected local corticosteroid within 12 weeks, Allergy to the solution that is using for PrT.
PRP	Acute/chronic musculoskeletal, cartilage and bone diseases; Chronic tendinopathies and enthesitis, Acute/chronic ligament injuries, Acute/chronic muscle tears and strains, Osteoarthritis, Osteochondritis dissecans, Arthroplasty operations, Meniscus injuries, Delayed fracture healing, Nonunions, Intervertebral disc injuries	Presence of tumors and metastatic disease, Active infection, Thrombocytopenia, Anemia, Pregnancy and lactation, Bowel thrombin allergy (if it is used as an activator)

Table 1.
Indications and contraindications of PrT and PRP applications.

follow-up of PRP [62]. PRP is superior to placebo in the treatment of early stage knee osteoarthritis. Interestingly, a similar improvement is observed between single and two doses of PRP [63] (**Figure 1**).

Indications and contraindications of PrT and PRP applications are shown in **Table 1**.

3. Conclusion

It is obvious that increasing of the regenerative injection treatment types will continue progressively in the future. At the present time, PrT can be used as a simple, reliable, fast-acting treatment method in patients resistant to conservative treatment. Although PRP is used for the same diseases as PrT, it can also be used in acute cases unlike PrT. Both methods can be used with confidence in pain management. Proper patient selection is the most important issue to obtain effective results from methods.

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