



Platelet-rich plasma injections: an emerging therapy for chronic discogenic low back pain

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Abstract: Autologous platelet-rich plasma (PRP) injections have been investigated in recent years as an emerging therapy for various musculoskeletal conditions, including lumbar degenerative disc disease. Although PRP has received increasing attention from medical science experts, comprehensive clinical reports of its efficacy are limited to those treating knee osteoarthritis and epicondylitis. Use of PRP is gaining popularity in the area of degenerative disc disease, but there is a clear need for reliable clinical evidence of its applications and effectiveness. In this article, we review the current literature on PRP therapy and its potential use in the treatment of chronic discogenic low back pain, with a focus on evidence from clinical trials.

Keywords: Platelet-rich plasma (PRP); chronic back pain; discogenic; disc degeneration

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Introduction

Discogenic low back pain

Low back pain is one of the major causes of physical disability affecting both older and younger people and can have enormous socioeconomic and health impacts. One of the major causes of low back pain is age-associated intervertebral disc degeneration (1,2), which affects the nervous system around the disc. Stimulation of the nociceptors in the annulus fibrosus causes pain, which is termed “discogenic” pain (3). Interestingly, degeneration, endplate injury and inflammation can stimulate pain receptors inside the disc, leaving the external disc intact (4). Intervertebral disc degeneration can be described as an active process involving changes in tissue and the cellular microenvironment that eventually lead to structural breakdown and impairment of intervertebral disc function (5).

Reported pathologic features of painful discs include the formation of zones of vascularized granulation tissue with

extensive innervation in annular fissures (6). Due to the avascular nature of intervertebral discs and, hence, their limited ability to regenerate, research on the regeneration of intervertebral discs and the various associated treatment methods has increased. Raj *et al.* [2008] (7) reported that various biochemical changes occur during disc degeneration, including loss of proteoglycan, loss of collagen fibers, increased fibronectin, increased enzymatic activity, increased fragmentation of collagen, proteoglycan and fibronectin, and changes in nutritional pathways. Histologic examination of painful discs has revealed the formation of a zone of vascularized granulation tissue extending from the nucleus pulposus to the outer part of the annulus fibrosus along the edges of the annular fissures, and growth of nerves deep into the annulus fibrosus and nucleus pulposus (8).

Disc degeneration is accompanied by changes in the matrixes of both the nucleus pulposus and the inner annulus fibrosus that are mediated by an inflammatory process (9).

Table 1 Current treatment methods for discogenic low back pain

Type of treatment	Details
Pharmaceutical	Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, tramadol, corticosteroids, opioids
Nonpharmacological	Physical therapy, osteopathic and chiropractic manipulation, yoga, tai chi, meditation, cognitive behavioural therapy with pain education, acupuncture
Interventional	Lumbar epidural steroid injections, thermal intradiscal procedures, spinal cord stimulation, spine surgery, intradiscal steroids, chemonucleolysis, intradiscal decompression, annuloplasty, use of intradiscal laser devices, intradiscal electrothermal therapy (IDET), Biacuplasty, discectomy, radiofrequency coblation, mechanical disc decompression

Nociceptive stimuli include pro-inflammatory cytokines produced by disc cells [such as interleukin (IL)-1, IL-4, IL-6, IL-8, IL-12, IL-17], interferon- γ , tumor necrosis factor (TNF)- α , downstream signaling molecules such as nitric oxide (NO), leukotrienes, prostaglandin E and by-products of disc cell metabolism such as lactic acid (9). Disc degeneration can also be caused by aging, apoptosis, vascular ingrowth, failure of nutrient supply to disc cells, abnormal mechanical loads or genetic factors (7,10). Rather than simply providing symptomatic relief, it is important to understand the pathophysiology of degenerated discs to determine the most effective treatment of the underlying cause.

Current treatments for discogenic back pain

As extensively reviewed by Raj *et al.* (7) and Simon *et al.* (11), a number of methods are used for the management of discogenic low back pain (Table 1). Since it is widely believed that degenerated discs are the source of discogenic pain, treatments mostly focus on surgical procedures such as fusion and total disc replacement. The reliability and effectiveness of these surgical procedures are still debated, as they are reported to only offer pain relief (9). Alternatively, non-invasive methods such as benign neglect, physical therapy or symptom control with medication or injection have been employed to treat discogenic pain. Notably, these

treatments do not improve the underlying degenerative condition, although they do resolve its symptoms (12). This clearly indicates the need for new therapies and/or interventions that actually treat the underlying causes of discogenic pain. Accordingly, increased attention has been given to emerging techniques such as growth factor therapy, and biomolecular and cellular treatments.

Previously reported *in vitro*, *in vivo* and clinical data clearly demonstrate the effectiveness and feasibility of biomolecular and cellular therapies for treating degenerative disc disease (13-15). Direct injection of growth factors into the annulus fibrosus and nucleus pulposus have resulted in clinically-proven improvement (16). Cellular and biomolecular treatments (which are in the clinical trial stage) combined with tissue engineering and annular repair (which are still in the preclinical stages) have been proposed to have great potential for the treatment of degenerative disc disease (17). Regenerative therapies for degenerated discs should focus on stimulating the production of the extracellular matrix or inhibiting the cytokines that upregulate matrix-degrading enzymes, which in turn may prevent loss of disc space height, increased loading on posterior elements and spinal stenosis (18).

Platelet-rich plasma (PRP)

PRP is defined as autologous blood with platelet concentrations above the physiological baseline. It is obtained by a centrifugation process which separates the liquid and solid components of blood (19,20). In recent years, PRP injections have gained considerable attention as a treatment method for musculoskeletal conditions due to their safety and ability to potentially enhance soft tissue healing. Tissue regeneration in musculoskeletal conditions is achieved by injecting PRP percutaneously. PRP has been effectively used for the treatment of rotator cuff tears, osteoarthritis of the knee, ulnar collateral ligament tears, lateral epicondylitis, hamstring injuries and Achilles tendinopathy (21). However, there is limited data showing its effectiveness for the treatment of intervertebral disc degeneration and low back pain. This article aims to shed light on the use of PRP for treating discogenic low back pain by reviewing the current clinical evidence in human applications.

Repairing effect of PRP

PRP is postulated to promote endogenous healing processes; however, the mechanism remains unclear. It is reported

that healing occurs after PRP stimulates the recruitment, proliferation and differentiation of cells involved in regeneration via a number of growth factors and proteins released from the platelets (22). Nonetheless, platelets contain antibacterial proteins and are capable of migrating to injury sites (23). The growth factors released by platelets include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor (TGF) β -1, platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF)-I, basic fibroblast growth factor (bFGF) and connective tissue growth factor (CTGF), which contribute significantly to tissue proliferation (22,24,25). These growth factors, produced by the concentrated platelets present in PRP, may restore the integrity of the extracellular matrixes of degenerating intervertebral discs (26). A key characteristic of these platelets is that they can release cytokines, chemokines and chemokine receptors and, thus, contribute to the regulation of inflammatory responses and immunological aspects of tissue healing. Platelets also prevent excessive leukocyte recruitment by anti-inflammatory cytokines (27).

PRP and intervertebral disc regeneration

How does PRP inhibit disc degeneration? Disc degeneration is a sequential process possibly starting with a circumferential tear in the annulus fibrosus that progresses to a radial tear, herniation, loss of disc height and resorption (28). In skin wound healing, platelets have the ability to bring disrupted cells closer together. Likewise, platelets pull the edges of degenerated disc tears together, leading to healing of cells. However, this is quite challenging due to the avascular nature of discs, which are not highly vascularized like skin (28).

Existing data on PRP and intervertebral disc degeneration include *in vitro* studies, *in vivo* studies, preclinical animal studies and human clinical trials. There is a large amount of evidence for the efficacy of the injection of growth factors for the treatment of intervertebral disc degeneration in animal models (14,29-33). PRP has also proven its efficacy *in vivo* in the improvement of disc height and disc hydration (17), which has enabled the technology to be used in human clinical trials. The remainder of this review will focus on clinical studies and human applications.

Clinical evidence for PRP treatment of back pain

Clinical evidence for PRP treatment of discogenic low

back pain in humans has been reported since 2011 (34). Since then, a limited number of clinical studies have demonstrated the effectiveness of PRP therapy (Table 2). In 2011, Akeda *et al.* (34) conducted a preliminary clinical trial demonstrating the safety and efficacy of intradiscal injection of autologous PRP as a biological therapy for degenerative disc disease. The study was performed on six patients who suffered chronic low back pain for more than three months. Degenerated discs were confirmed by magnetic resonance imaging (MRI) and standardized provocative discography. At six months follow-up, patients showed a significant decrease in mean pain score and no adverse events were reported post-treatment.

Bodor *et al.* [2014] studied 35 patients who were given 47 disc injections of PRP in the lumbar and thoracic spine (28). Two-thirds of the patients showed positive outcomes. The authors also presented a detailed case series of five patients with discogenic back pain treated with PRP injections. The follow-up period ranged from ten days to 10 months, in which patients exhibited substantial improvements in pain that enabled them to return to normal physical activities. Despite two patients having vasovagal episodes, there were no complications or side effects related to this treatment.

In 2016, Levi *et al.* published data from a prospective clinical trial on 22 patients examining the effect of intradiscal PRP injection on discogenic back pain (35). No complications or serious side effects were reported. Back pain was measured using a visual analogue scale (VAS) and Oswestry Disability Index (ODI). After a 6-month follow-up period, 47% of patients reported at least a 50% improvement in pain and a 30% improvement in their ODI score. The authors speculate that the time frame required for the treatment to take effect, possible adverse effects from the anesthetics and antibiotics used during the procedure, and the PRP preparation method used, account for the lack of a significant positive outcome in this study. In another study by Navani and Hames [2015], six patients were given a single injection of 1.5–3 mL of autologous PRP (36). At a 24-week follow-up, patients reported a 50% decrease in pain according to the verbal pain scale (VPS), with no adverse effects reported.

In 2016, Hussein and Hussein performed a clinical trial on 104 patients with chronic low back pain (37). Unlike the studies mentioned earlier in this section, platelet leucocyte-rich plasma (PLRP) was used instead of PRP, owing to the phagocytic nature of leucocytes. Injections were carried out weekly for 6 weeks. The method was proven to be a safe and effective method for relieving chronic low back pain,

Table 2 Summary of clinical evidence on platelet rich plasma for the treatment of discogenic low back pain

Type of study	Number of patients in the study	Volume of PRP injected	Starting volume of whole blood	Number of injections during the study period	Study period	Pain scores evaluated in the study	References
Preliminary clinical trial	6	2 mL	200 mL	Single	6 months	VAS and RDQ	Akeda <i>et al.</i> , 2011 (34)
Case series	35	1.25–2 mL	9 mL	–	10 days to 10 months	Oswestry score	Bodor <i>et al.</i> , 2014 (28)
Prospective trial	22	1.5 mL	35 mL; 60 mL	Single, at one or multiple levels	6 months	VAS and ODI	Levi <i>et al.</i> , 2015 (35)
Case series	6	1.5–3 mL	60 mL	Single	24 weeks	VPS	Navani and Hames, 2015 (36)
Clinical trial	104	2.5–5 mL	50 mL	6	12–18 months	NRS (range, 0–10) and ODI	Hussein and Hussein, 2016 (37)
Double-blind randomised controlled clinical trial (DBRCT)	47	1–2 mL	30 mL	Single, at one or multiple levels	8 weeks	FRI, NRS-Best Pain, the SF-36, and the modified NASS satisfaction scores	Tuakli-Wosornu <i>et al.</i> , 2016 (38)
Pilot study	10	5 mL	100 mL	Single	3 months	VAS scores, MODQ index and SLRT	Bhatia and Chopra, 2016 (39)
Prospective preliminary clinical trial	14	2 mL	200 mL	Single	10 months	VAS score and the physical disability score (RDQ)	Akeda <i>et al.</i> , 2017 (40)
Single case report	1	–	–	Single	12 months	–	Lutz, 2017 (41)
Open label study	15	–	–	Single	12 months	Flexion, VAS, and pain scores according to the PPI, SF-12 and DPQ	Comella <i>et al.</i> , 2017 (42)

–, not specified. VAS, visual analogue scale; RDQ, Roland-Morris Disability Questionnaire; ODI, Oswestry Disability Index; VPS, verbal pain scale; NRS, Numeric Rating Scale; FRI, Functional Rating Index; NASS, North American Spine Society; MODQ, Modified Oswestry Disability Questionnaire; SLRT, Straight Leg Raising Test; DPQ, Dallas Pain Questionnaires; PPI, present pain intensity; SF, Short Form.

with a success rate of 71.2% reported by the authors. No adverse effects or complications were reported other than short-term pain at the injection site.

The first double-blind randomized controlled trial (RCT) of intradiscal PRP therapy was performed by Tuakli-Wosornu *et al.* in 2016 on 47 participants with chronic lumbar discogenic pain (38). Participants with a history of chronic axial low back pain were recruited and were randomly allocated to treatment or control groups at a 2:1 ratio, respectively. At an 8-week follow-up, outcomes were measured by Functional Rating Index (FRI), Numeric Rating Scale (NRS)-best pain, the Short Form (SF)-36,

and modified North American Spine Society (NASS) satisfaction scores. The study found statistically significant improvements in the treatment group, and the effects of PRP were sustained for a period of at least 1 year according to FRI scores. No complications were reported.

In a pilot study performed on ten patients in 2016 by Bhatia and Chopra, PRP injections were shown to improve pain (39). Patients suffering from chronic prolapsed intervertebral discs were given single 5 mL injections of autologous PRP and were followed up after 3 months. Improvement in pain was evaluated using VAS, the Modified Oswestry Disability Questionnaire (MODQ)

Table 3 Ongoing clinical trials to study the effect of platelet-rich-plasma for the treatment of discogenic low back pain (unpublished data)

Study sponsor/PI	Trial identifier number	Type of trial
Shanghai Changzheng Hospital	NCT02983747	Single-blind randomised
Pei-Yuan Lee	NCT03197415	Single group assignment
Star Spine and Sport	NCT03122119	Non-randomised parallel assignment

PI, primary investigator.

index and Straight Leg Raising Test (SLRT). All patients had a gradual improvement in symptoms that persisted for at least three months without any complications.

In 2017, Akeda *et al.* conducted a clinical study investigating the safety and feasibility of autologous PRP releasate injections for discogenic low back pain (40). PRP releasate is a form of bioactive soluble factors isolated from activated PRP that can stimulate tissue repair. The authors implicated that the platelets were isolated by the buffy coat (BC) method and therefore contained lower concentrations of pro-inflammatory cytokines; hence, the sample was considered as “pure PRP”. This prospective, preliminary clinical study was carried out in 14 patients with lumbar discogenic low back pain for a period of 10 months. Seventy-one percent of patients showed a 50% reduction in pain as measured by VAS scores; however, low back pain returned in two patients. In contrast to the VAS scores, physical disability scores [Roland-Morris Disability Questionnaire (RDQ)] were significantly reduced in 79% of patients. Apart from temporary leg numbness in two patients, no other notable adverse events were reported. In summary, this study proved the safety, feasibility and efficacy of PRP in the treatment of lumbar discogenic back pain.

A single case report by Lutz [2017] reported on the effectiveness of intradiscal PRP injection for improving low back pain and function (41). The patient was diagnosed with a degenerated disc and had received an ineffective caudal epidural steroid injection and physical therapy. The patient was given a single PRP injection and showed considerable improvement in pain and motion after 6 weeks. At a 1-year follow-up, there was remarkable improvement in low back pain and the patient was able to return to athletic activities.

The clinical studies discussed so far in this review demonstrate the efficacy of autologous PRP when applied alone in the treatment of chronic back pain. Therefore, a report which shows the effect of PRP injection together with another agent [stromal vascular fraction (SVF)] is particularly interesting. Comella *et al.* investigated the safety and efficacy of PRP in combination with SVF delivered into

the disc nucleus of patients with degenerative disc disease (42). SVF is a mixture of adipose-derived stem cells (ADSCs) and growth factors. The study proved to be safe and successful with significant improvements in flexion, VAS, and pain scores according to the Present Pain Intensity (PPI) scale, SF-12 and Dallas Pain Questionnaires (DPQ). The majority of patients reported remarkable reductions in pain compared to baseline over a period of 6 months post-injection. The only side effects reported were soreness in the abdomen from liposuction (for SVF) and soreness in the back from the PRP injection, both of which resolved within 1 week.

Unpublished clinical data

A search of unpublished and ongoing clinical work identified three clinical trials evaluating PRP injections for the treatment of low back pain. The details of these studies are presented in *Table 3*.

Discussion

This review aimed to summarize results from both published and unpublished clinical trials of PRP therapy used in the treatment of discogenic low back pain. The majority of the published clinical studies have applied PRP injections for knee osteoarthritis and epicondylitis, with few reporting its effectiveness for discogenic low back pain. Interestingly, the clinical studies presented here clearly demonstrate the growing interest in PRP injections for treating back pain, with the number of published clinical studies increasing in the past few years. However, it should be noted that there is a lack of RCTs among the reviewed studies (*Table 2*).

The clinical studies that used PRP injections as a therapy for discogenic low back pain reported good results overall. A major and notable advantage of the therapy is the safety of the autologous PRP itself, which does not cause any major complications. Other than a few temporary side effects (soreness at the injection site, numbness in legs), none of the

studies reported any serious adverse events or complications resulting from the injections. Because autologous PRP is obtained from the patient's own blood, PRP therapy carries low risks of disease infection and allergic reaction (43). In addition, it has been reported that PRP has antimicrobial properties (44,45), which in turn could reduce postsurgical infection risk.

Research on PRP therapy has demonstrated remarkable improvements in pain intensity according to a variety of pain scores. The clinically-beneficial effects have enabled patients to return to normal physical activity (28,41). Notably, the number of injections (single, multiple or at multiple levels), volume of PRP injected (1–5 mL), initial whole blood volume (9–20 mL) and follow-up periods (8 weeks–18 months) varied across the studies. The PRP isolation procedures used in the studies described in this review remained fairly similar. They involved centrifugation of the patients' whole blood and use of a commercial kit or in-house technique.

Even though the clinical application of PRP injection for degenerated discs is gaining popularity, an important aspect which needs to be considered is the age of the target population. The impact of age on the effectiveness of growth factor injections has been previously discussed (14). Likewise, a low number of functional cells in the intervertebral discs of older patients may hinder the efficacy of PRP injections. The PRP therapy will be more efficient if applied before disc degeneration reaches an advanced stage. Another possible approach will be the use of PRP in combination with cellular therapy, such as the use of nucleus pulposus cells.

The cost-effectiveness of PRP therapy remains controversial. In 2013, Hsu *et al.* reported that it is more expensive than steroid injections when used in the short-term, but potentially less expensive when used for long-term treatment (20). On the other hand, PRP therapy is widely described as cost-effective as it is autologous in nature, simple to prepare and readily available (33,46,47).

Future directions in PRP therapy include conducting more randomized, controlled and unbiased clinical trials to provide higher quality evidence (48). To the best of our knowledge, only a single randomized controlled clinical trial has been conducted on the effectiveness of PRP injections on discogenic low back pain (38). Further research is necessary to investigate the long-term effects of PRP injections, including possible adverse effects, over longer follow-up periods. A possible future clinical direction would be to compare single and multiple injection regimes

within the same study. Other aspects such as the method of preparation of PRP including starting whole blood volume, platelet concentration, PRP composition and amount of PRP injected can be further investigated. Additional research on the above aspects will be advantageous to clinicians in providing better guidance and indications for determining individual patient-based treatment plans and, thus, better clinical outcomes.

Conclusions

In this review, we described clinical evidence from the literature and presented an update on the use of PRP therapy for the treatment of discogenic low back pain. It is evident from our review that PRP is a safe, effective and feasible treatment modality and is evolving as a powerful therapy for the treatment of discogenic back pain. Considering the remarkable progress made already, and the other potential aspects which remain for further investigation, PRP therapy undoubtedly offers new and exciting prospects for the treatment of degenerative disc disease and other musculoskeletal disorders.

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Footnote

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