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Role of platelet Rich Plasma (PRP) in Chronic prolapsed intervertebral disc

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Abstract

Lumbar radiculopathy is a major health problem often treated by surgery or guided lumbar epidural steroids for pain relief. 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. In this article we used Platelet Rich Plasma (PRP) a novel therapeutic tool of autologous nature that has emerged strongly in recent years to treat patients of prolapsed intervertebral disc.

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

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]. 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(Lk), prostaglandin E(Pg-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

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

1. 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.

Table 1: Current treatment methods for discogenic low back pain

Type of treatment	Details
Pharmaceutical	Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, tramadol, corticosteroids, opioids
Non-pharmacological	Physical therapy, osteopathic and chiropractic manipulation, yoga, tai chi, meditation, cognitive behavioral 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, intradisclectrothermal therapy (IDET), Biacuplasty, discectomy, radiofrequency coblation, mechanical disc decompression

Platelets contain antibacterial proteins and are capable of migrating to injury sites [12]. 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 [12, 14, 15]. These growth factors, produced by the concentrated platelets present in PRP, may restore the integrity of the extracellular matrixes of degenerating intervertebral discs [16].

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 progress to a radial tear, herniation, loss of disc height and resorption [18]. 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 [18].

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, 19-23]. 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 [29]. Since then, a limited number of clinical studies have demonstrated the effectiveness of PRP therapy (Table 2). In 2011, Akeda *et al.* [29] conducted a preliminary clinical trial demonstrating the safety and efficacy of intra-discal 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 [30]. 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 [31]. 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 [32]. 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. 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

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]. 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].

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A large number of publications for PRP in field of

orthopaedics and sports medicine has been focused on tendon injuries including patellar tendinosis (jumper's knee), lateral epicondylitis (tennis elbow), Achilles tendinopathy, osteoarthritis, plantar fasciitis, anterior cruciate ligament and rotator cuff arthroscopic repair [35, 36].

Since Himalayan Institute of Medical Sciences is a tertiary care centre, a large number of patients present to the outpatient department with complaints of chronic low back pain due to intervertebral disc prolapse. Many of them have not responded to conventional oral, local medications and also do not prefer surgery due to lack of finances or apprehension or had failed back surgeries. Such patients are referred to us for epidural analgesia.

Very few studies [34, 37] are available on the use of PRP in lumbar epidural space but considering its vast potential, safety and encouraging results it was decided to use it as a modality for pain relief in such patients as an alternative to steroids.

Materials and Methods

The pilot study was carried out in the Department of Orthopaedics, Shri Ram Murti Smarak Institute of Medical Sciences, Bhojipura Bareilly over a period of 6 months between September 2019 and February 2020 with due approval of ethics committee. This study included patients with findings of lumbar disc herniation/prolapse in MRI, of either sex with age less than 65 years, having complaints of backache + radiculopathy for more than 4 weeks duration with a positive Straight Leg Raising Test (SLRT) and not responding to the conventional treatment.

Patients presenting for facet joint injection between September 2019 and February 2020. Exclusion criteria included patient refusal, sepsis at site of injection, any spinal deformity or fracture, raised intracranial pressure, bowel bladder involvement, coagulation disorders, fever, sepsis and use of corticosteroids by mouth or intravenous within two weeks of PRP procedure.

After fulfilling the criteria, patients were explained in detail about the treatment modality & a written informed consent was taken. Diagnostic work up included complete haemogram with ESR, coagulation profile, blood sugar, X-Ray Spine (AP and lateral view). Patients were kept nil per oral 4 hours before the procedure. Baseline Visual Analogue Scale (VAS) score [39], Modified Oswestry Disability Questionnaire (MODQ) [39], SLRT [38] and neurological examination of lower limb prior to the procedure was recorded. PRP was prepared under aseptic condition from patient own blood. About 100ml of patients own blood was taken which was centrifuged and 5ml of platelet rich plasma was prepared in blood bank.

Under strict aseptic precautions a single injection of 5ml autologous PRP was administered in the facet joint with 18G tuohys needle using fluoroscopic guidance. After the procedure haemodynamic parameters were monitored and recorded every 5 minutes for 30 minutes and also for any possible complications.

Patients were evaluated after 1 hour of procedure and discharged with advice to avoid too much bending, lifting heavy weight or walking long distances and told to follow-up at 3 week and 3 month. VAS score, MODQ and SLRT were noted at all times. Neurological examination of lower limb was also done which included motor examination in form tone, power, reflexes and sensory examination.

Results

It was seen in our study that 20 patients who underwent

autologous PRP injection via lumbar epidural showed a gradual improvement of symptoms in terms of VAS scores, MODQ index and SLRT. This gradual improvement of symptoms was sustained through a period of 3 months till the patients were followed up. Apart from two patients whose VAS score was 5, rest of them showed improvement and their VAS SCORE was 4 or less than 4 at three months of follow up. More than half of the patients MODQ score was less than or equal to 30% and SLRT improved to >70 at three months in most of the patients. It showed that the gradual improvement seen was sustained till the follow-up period of 3 months. There were no complications seen and patients were able to do their daily activities without use of pain medications.

Table 2: Modified Oswestry disability questionnaire score. 0% to 20% - minimal disability; 21% to 40% - moderate disability; 41% to 60% -severe disability; 61% to 80% - crippled; 81% to 100% - bed bound

Patient no.	Pre procedure	After 1 hr	Follow up 3 weeks	Follow up 3 months
1	35-70	35-70	>70	>70
2	<35	<35	35-70	35-70
3	35-70	35-70	35-70	>70
4	35-70	35-70	>70	>70
5	<35	<35	35-70	35-70
6	<35	<35	35-70	35-70
7	35-70	35-70	35-70	>70
8	<35	<35	35-70	35-70
9	<35	<35	35-70	35-70
10	35-70	35-70	35-70	>70
11	35-70	35-70	>70	>70
12	<35	<35	35-70	35-70
13	<35	<35	35-70	35-70
14	35-70	35-70	>70	>70
15	35-70	35-70	35-70	>70
16	<35	<35	35-70	35-70
17	35-70	35-70	35-70	>70
18	<35	<35	35-70	35-70
19	35-70	35-70	35-70	>70
20	<35	<35	35-70	35-70

Table 2: Straight leg raising test scores. Pain upto 35 degree is diagnostic of PIVD; 35 – 70 degree is suggestive of disc prolapsed; Pain beyond 70 degree is equivocal

Patient no.	Pre procedure	After 1 hr	Follow up 3 weeks	Follow up 3 months
1	40%	40%	32%	30%
2	58%	50%	45%	32%
3	42%	40%	40%	28%
4	60%	60%	50%	35%
5	55%	55%	50%	38%
6	45%	45%	40%	20%
7	48%	45%	40%	30%
8	55%	50%	50%	26%
9	50%	50%	40%	30%
10	65%	65%	50%	32%
11	40%	40%	38%	20%
12	50%	50%	40%	22%
13	60%	60%	50%	25%
14	46%	46%	40%	20%
15	52%	50%	45%	30%
16	46%	46%	40%	28%
17	50%	50%	45%	35%
18	55%	55%	50%	38%
19	40%	40%	32%	26%
20	48%	48%	42%	30%



Fig 1: Pretreatment and post treatment

Table 3: Patient no. Pre procedure After 1hr

Patient no.	Pre procedure	After 1 hr	Follow up 3 weeks	Follow up 3 months
1	5	5	4	3
2	6	6	5	4
3	5	5	4	4
4	7	6	5	4
5	8	7	5	5
6	7	6	5	4
7	8	7	5	4
8	8	7	6	4
9	5	5	4	3
10	6	6	4	4
11	6	5	4	3
12	5	5	4	3
13	8	7	5	5
14	7	6	4	4
15	7	7	4	3
16	6	6	5	3
17	8	7	5	4
18	5	5	4	3
19	5	5	4	3
20	6	5	4	4

Discussion

PRP is defined as a sequestration and concentration of platelets within the plasma fraction of autologous blood. The rationale behind the use of PRP is the deliver a high concentrations of growth factors and cytokines which can improve the healing process [3]. Each platelet contains 50 to 80 alpha granules which have more than 30 bioactive proteins. These proteins play an essential role in haemostasis and hard and soft tissue healing. Platelet counts of 150,000 to 300,000/microL are considered normal Alpha granules contain numerous proteins and peptides that help in cellular migration and growth including platelet derived growth factor (PDGF), transforming growth factor (TGF-beta), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet factor 4, interleukin-1 (IL-1), platelet derived angiogenesis factor, platelet derived endothelial growth factor, epithelial cell growth factor, osteocalcin, osteonectin, fibrinogen, vitronectin, fibronectin and thrombospondin. PRP count of 1,000,000 microL is regarded as the benchmark for PRP. PRP causes a three to five fold increase in platelet concentration over baseline and exogenous delivery of activated PRP leads to platelet aggregation and clotting after approximately 10

minutes and within 1 hour approximately 95% of the alpha granule contents have been secreted [3]. The motive behind use of PRP is to increase the concentration of activated platelets at the site of chronic injury which restarts the inflammatory phase, leading to healing.

Our results are consistent with study done by Akeda et al., [9]. They injected PRP into the discs of patients having chronic low back pain and Degenerative Disc Disease in one or more lumbar segments. Improvement was seen in VAS scores from 6.7 to 3.7, $p < 0.01$ and it was sustained over a period of 6 months [9].

Similarly Bodor et al., reported positive effects to single intradiscal PRP which were sustained for a period of 6-12 months in almost 2/3rd of patients. Half of them had “excellent” and half “good” response on the basis of pain resolution and ability to return to activities of daily living and exercise [10].

In our technique we have used interlaminar approach for injecting PRP in epidural space which involves passage of a needle through ligamentum flavum. Interlaminar epidural injections have been studied extensively regarding their role in radicular pain due to disk herniation, pain due to spinal stenosis, axial back pain in the absence of disk herniation and failed back surgery syndrome. Advantages include the increased likelihood that injected PRP will reach adjacent spinal levels, the ability to treat bilateral pain and the need for a lower volume of PRP. There appears to be a good evidence for the treatment of radicular pain due to disk herniation and somewhat weaker evidence for treatment of spinal stenosis, discogenic pain and postsurgical pain with this technique.

Conclusion

In this study 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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