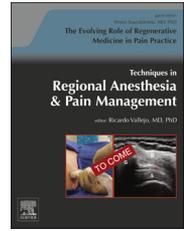


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Platelet-rich plasma injections for lumbar discogenic pain: A preliminary assessment of structural and functional changes

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ABSTRACT

The goal of this case review is to evaluate functional and structural changes with the use of intradiscal PRP in patients with lumbar discogenic pain. The secondary outcomes include improvement in pain, medication use, hospitalization, and surgery. Low back pain affects a large portion of the population causing a major social and economic effect. Current interventional treatments remain inadequate and transient targeting the symptoms without addressing the underlying cause. Platelet-rich plasma (PRP) has been used clinically in various settings for its healing properties attributed to growth factors. A total of 6 patients with chronic discogenic low back and leg pain who tried and failed conservative treatments were administered a single injection of 2-mm autologous PRP into the nucleus pulposus after careful study of the disk anatomy via discography and computed tomography scan. The patients were followed up at 2, 4, 8, 12, 16, 20, and 24 weeks; postinjection and primary and secondary outcomes were recorded. Verbal pain scale score for pain of all patients decreased more than 50% and their function increased for the period of 6 months and beyond. Postprocedure magnetic resonance imaging documented positive structural changes in small percentage of patients. None of the patients presented to the hospital or received surgery after this treatment. Although our preliminary results have been promising, well-designed randomized controlled trials are warranted to understand the full breath of the efficacy, risks, and complications from the use of PRP in the disk.

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Introduction

Low back pain affects a large proportion of the population and has major social and economic costs. In 2007, approximately 27 million adults, or 11.9% of adults aged 18 years

and older, reported having back problems, of which, approximately 19 million adults reported receiving treatments.¹ Total direct cost of chronic low back pain-related health care utilization is estimated to be \$96 million a year.² Discogenic lower back pain is the most common cause of chronic lower

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Table 1 – Inclusion and exclusion criteria for participation.

Inclusion criteria	Exclusion criteria
Discogenic low back pain for ≥ 6 months	Patient refusal
Failure of conservative treatment measures	Presence of a known bleeding disorder
Intervertebral disk height of at least 50%	Pregnancy
Degenerated disks, annular tears or contained disk protrusion on postdiscography computed tomography scan	Systemic or local infection
Concordant pain on discography	Presence of an unstable medical or psychiatric condition
	Severe spinal canal stenosis at the level of injection
	Extruded or sequestered disk

back pain, accounting for 39% of cases. The disk pathology accounts for 30% of cases and other causes, such as zygapophysial joint, musculoskeletal pain, and others have lower prevalence rates.³

The disk damage ranges from disk degeneration to disk extrusion and sequestration. Current interventional treatments remain inadequate and transient and target the symptoms without addressing the underlying cause. Recent efforts are being directed toward development of therapies that aim at alleviating pain through the restoration of intervertebral disk (IVD) structure and function. In our effort toward exploring safe and effective intradiscal biologic therapies, we present to you the first ever case series of intradiscal injection of autologous, platelet-rich plasma (PRP). The primary goal in this case series was to demonstrate safety and efficacy of PRP in the disk space. The secondary outcomes included change in function, utilization of health care services, hospitalization, and spine surgery.

Materials and methods

A total of 6 patients with chronic low back and leg pain who had tried and failed conservative treatments were administered a single injection of autologous PRP into the nucleus pulposus.

The procedures including risks and benefits were explained in details to each patient. After informed consent, the patients underwent discography using dual needle technique with an 18-gauge introducer and 22-gauge follow-through needle. This was followed by postdiscography computed tomography (CT) scans. The patients meeting the inclusion criteria were offered the treatment (Table 1). All disk procedures were performed in an operating room under fluoroscopic guidance with complete aseptic precautions, including prophylactic antibiotics and proper surgical prep and drape technique. PRP was obtained using 60 mL of whole blood centrifuge to yield 6 mL of PRP using Emcyte Pure PRP system. Approximately, 2 mL (range: 1.5–3 mL) of PRP was injected into each disk until increased pressure was felt in the plunger and solution could not be injected easily. No more than 3 disks were injected for any given patient. No activating or additive agents were used with PRP.

After the injection, the patients were observed in the recovery room for 30–40 minutes and then discharged home in stable condition with detailed postoperative instructions. They were followed up per protocol every 2–4 weeks until

6 months postinjection. Postoperative instructions included 4 weeks of rest with bracing followed by progressive lumbar mobilization exercises until they reached their full functional potential.

Case 1

A 54-year-old administrative assistant with chronic low back with right lower extremity posterior radicular pain along L5 dermatome to the foot for 4 years. Magnetic resonance imaging (MRI) revealed disk bulge at L4–5 with mild caudal neural foraminal encroachment. Electrodiagnostic study showed right L5, S1 denervation. The patient received right lumbar epidural steroid injection with relief for 2–3 weeks but developed side effects of flushing and swelling.

We performed provocative discography at L2–3, L3–4, and L4–5 levels and noted concordant pain at L4–5 level. Postdiscography CT revealed grade 4 annular tears at L2–3, L3–4, and L4–5 levels (Figure 1A and B). The patient was injected with 2 mL of PRP at the 3 levels to avoid exploratory surgery (Figure 1C and D).

The radicular pain resolved in 2 weeks and verbal pain scale (VPS) steadily decreased from 5/10 preprocedure to 0–1/10 in 3 months and ongoing. The MRI 6 months later showed mild disk bulging at L4–5, minimal at L3–4 with no evidence of central or foraminal stenosis.

Case 2

A 55-year-old female avid runner with a history of right leg 10/10 pain for 6 months from bending at the waist while making the bed. The pain affected her physical and emotional life impairing her ability to perform household chores, driving, walking, and causing depression and anxiety.

She had positive straight leg test at 40°. MRI showed right paracentral disk protrusion with right L5 and S1 neural foraminal narrowing. She underwent lumbar epidural steroid injection with 75% relief for 3–4 weeks. Postdiscography CT demonstrated L4–5 and L5–S1 grade 3–4 annular tears with mild to moderate central canal narrowing. The patient was injected with 2 mL of PRP at L4–5 and L5–S1 disks per protocol. Her VPS decreased from 8/10 preprocedure to 3/10 in 2 weeks, and 0–1/10 in 12 weeks with resolution of right leg radicular pain. She returned to running. The 6-month follow-up MRI demonstrated improvement of posterior annular tear at L4–5 (Figure 2C and D).

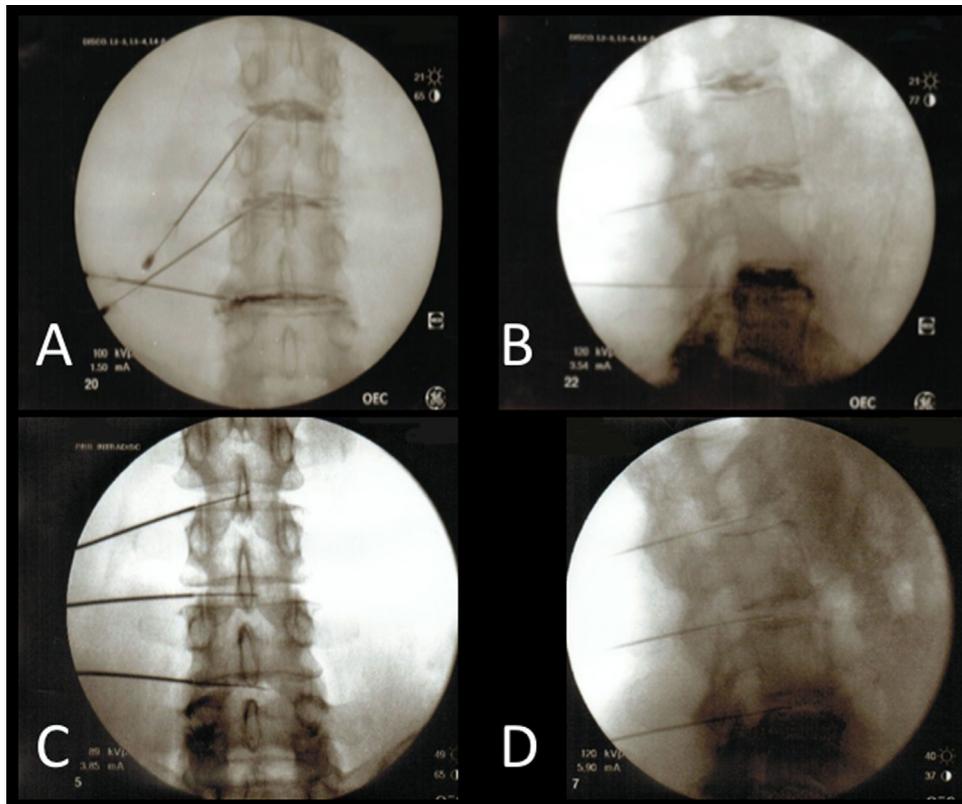


Fig. 1 – Discography demonstrating disk disruption in anterior-posterior (A) and lateral (B) views at L2-3, L3-4, and L4-5 levels. Anterior-posterior (C) and lateral views (D) demonstrating needle placement for intradiscal PRP injection at L2-3, L3-4, and L4-5 levels. (Color version of figure is available online.)

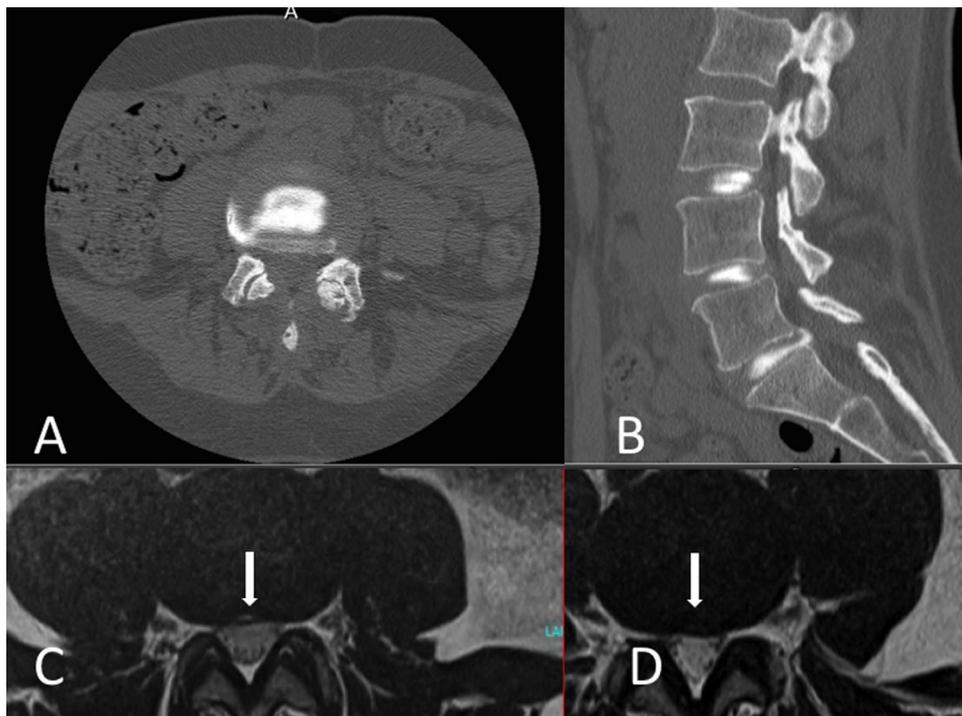


Fig. 2 – Sagittal (A) and axial (B) views of CT scan postdiscography demonstrating grade 4 annular tear at L5-S1. The MRI axial views preinjection (C) and 6 months post-PRP injection (D) demonstrating annular tear (C, white arrow) improvement (D, white arrow) of annular tear at L4-5 level. (Color version of figure is available online.)

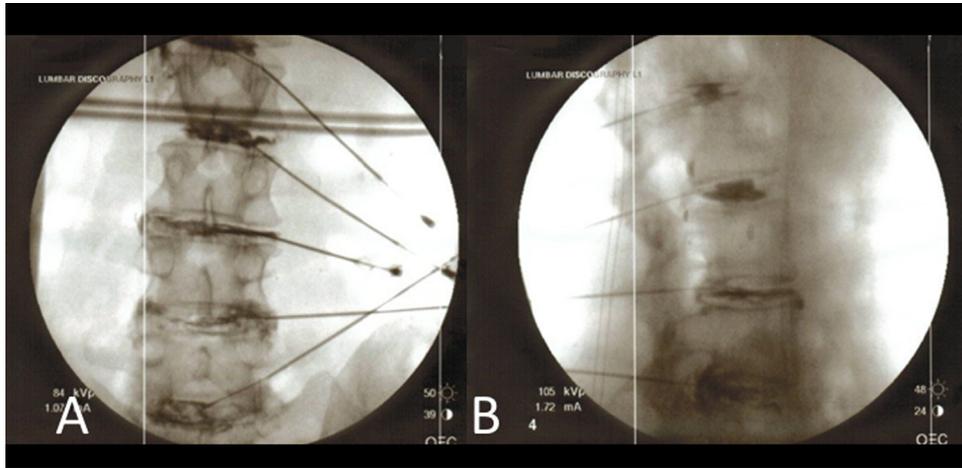


Fig. 3 – Discography demonstrating disk disruption in anterior-posterior (A) and lateral (B) views with annular tears at L1-2 and L2-3 and high-grade disk disruption L3-4, L4-5, and L5-S1 levels. (Color version of figure is available online.)

Case 3

A 44-year-old female with history of left-sided low back and extremity pain for 7 months since lifting her left leg to wear her clothes. She has positive straight leg raise at 60°. MRI demonstrated disk disruption at all levels, which is with facet arthropathy with disk facet causing bilateral neural foraminal encroachment at L3-4, L4-5, and L5-S1. Discography was conducted at from L1-L2 through L5-S1 and revealed concordant pain at L4-5 and L5-S1 disk. Postdiscography CT demonstrated protrusions at L3-4, L4-5, and L5-S1 and annular tears at L1-2 and L2-3 with moderate left neural foraminal narrowing at L3-4, L4-5, and L5-S1 (Figure 3). PRP

was injected at L3-4, L4-5, and L5-S1 disks. She reported decrease in pain from preprocedure VPS 4-5/10 to 3/10 in 2 weeks and 0/10 from 4 months onwards. She is back to doing boot camps and running 3 miles 2-3 times/wk.

Case 4

A 54-year-old Japanese male with a history of right low back and bilateral lower extremities tingling- numbness pain from no specific inciting incident. He has tried and failed physical therapy, medications, epidural steroid injections. MRI Lumbar spine revealed multilevel retrolisthesis and disk degeneration with annular tears from L2 through L5 levels. Also contained

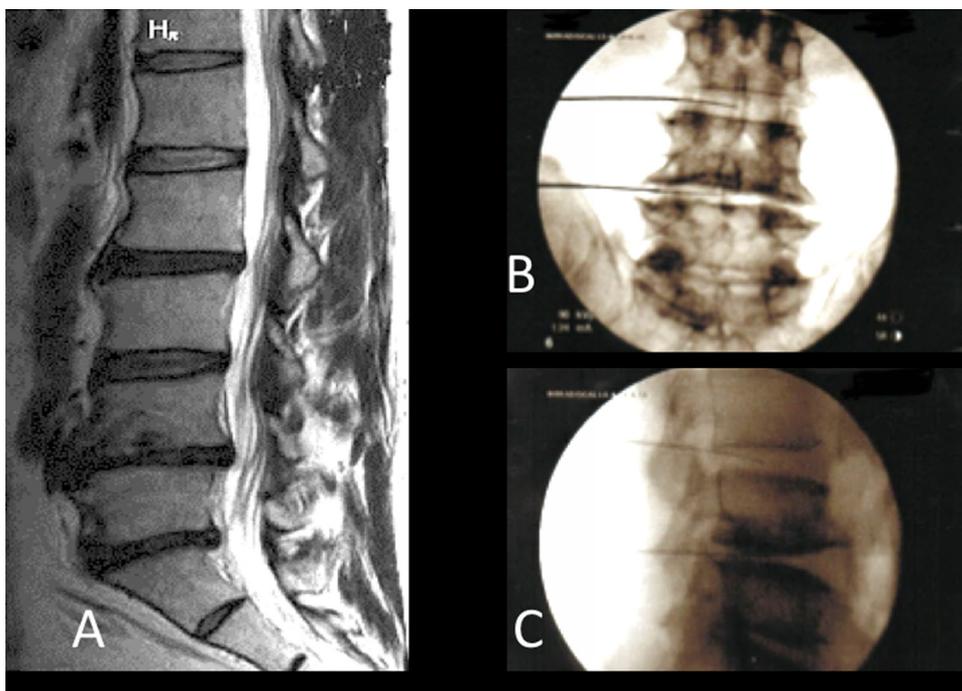


Fig. 4 – MRI images (A) identifying ongoing multilevel degenerative changes from L2-3 to L5-S1. Anterior-posterior (B) and lateral (C) views demonstrating needle placement for intradiscal PRP injection at L3-4 and L4-5 levels. (Color version of figure is available online.)



Fig. 5 – Sagittal view of CT scan postdiscography demonstrating disk disruption at L3-4, L4-5, and L5-S1. (Color version of figure is available online.)

L4-5 disk extrusion with right L5 and L3-4 disk protrusion with right L3 nerve compression (Figure 4). Postdiscography CT scan demonstrated extension of contrast material into annulus indicating tears at L2-3, L3-4, and L4-5. He underwent PRP injection at L3-4 and L4-5 disks with 3 mL of PRP in each disk (Figure 4B and C). He reported soreness for 1-2 days but no pain after that even with activities that used to cause pain before. His VPS decreased from 2-4/10 preprocedure to 0/10 in 4 weeks and ongoing.

Case 5

A 42-year-old male with a history of low back pain and numbness of the left fourth digit for 4 years from an injury while

playing soccer. The MRI revealed far left disk extrusion at L2-3 impinging on the left L2 nerve root, small disk protrusion at L3-4 and L4-5. He underwent discography at L3-4, L4-5, and L5-S1; and CT revealed disk bulge with grade 5 annular tear at L4-5, grade 4 at L3-4 and grade 2 at L5-S1 (Figure 5). He underwent intradiscal PRP injection at L3-4, L4-5, and L5-S1 with stiffness for 4 weeks followed by 50% decrease in pain and increase in his physical activities.

Case 6

A 38-year-old female with history of low back and bilateral lower extremities pain for the past 8 years. The pain started insidiously with sudden disk herniation causing loss of control of her right leg 6 years ago. The symptoms self-resolved and returned after a few years. She had positive bilateral straight leg raise test at 30°. MRI of the lumbar spine demonstrated herniation at L3-4 and L5-S1 and disk bulge with annular tear at L4-5. Discography was conducted at L3-S1 levels and CT scan revealed annular tears at L4-5 and L5-S1 and contained disk protrusion at L3-4 (Figure 6).

PRP injections were done at L3-4, L4-5, and L5-S1 levels. She reported significant soreness after the injection for 4 weeks followed by steady decrease in pain to 50% at 12 week mark and onwards.

Results

The patients were followed up in the clinic at 2, 4, 8, 12, 16, 20, and 24 weeks. At each visit, their VPS, SF-36, side effects, adverse reactions, complications, hospitalization, emergency room visit, and surgery was tracked. VPS decreased by 50% for every patient. No adverse effects were noted in any patient.

All patients improved by 3 months postinjection and maintained low pain levels not requiring any additional treatments for 6 months postinjection. SF-36 demonstrated

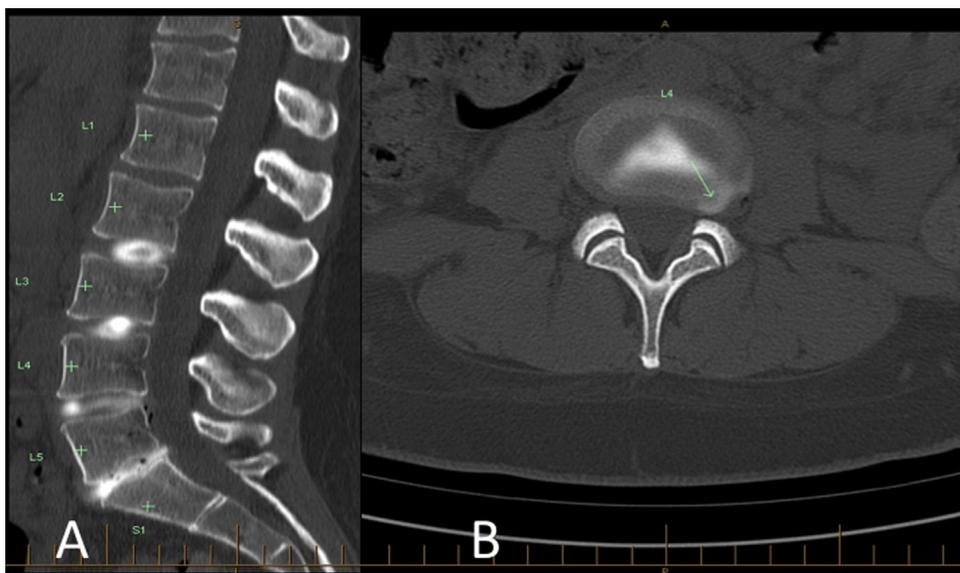


Fig. 6 – Sagittal (A) and axial (B) CT scan views postdiscography demonstrating grade 4 annular tear (white arrow) at L4-5 and L5-S1 in sagittal and L4-5 in axial views. (Color version of figure is available online.)

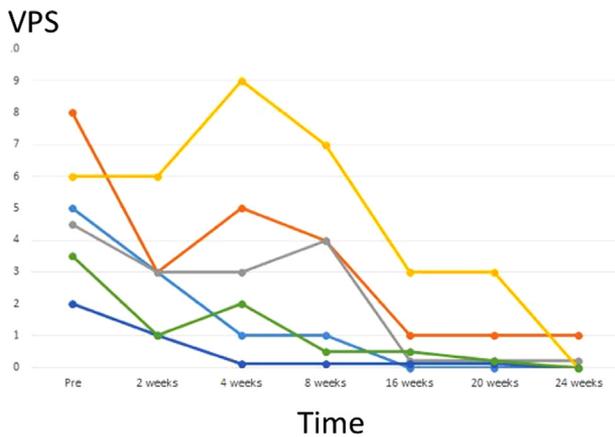


Fig. 7 – Graph demonstrating change in verbal pain scores (VPS) over 24 weeks. (Color version of figure is available online.)

improvement in both physical component summary scores and mental component summary (MCS) scores in all patients. None of the patients presented to the emergency room, got hospitalized, or received surgery for the spinal area treated with the PRP injection. One patient required treatment of her cervical spine although her lumbar spine treated with PRP was much better. No increase in medication use was noted in any patient pertaining to the spinal area treated 4 weeks postinjection; in fact, most patients started tapering of their pain medication within 2 weeks of injection. MRI completed 6 months postinjection demonstrated positive structural changes in 2 out of 6 patients (Case 1 and Case 2). The graphs depicting changes in VPS, SF-36 (physical component summary and mental component summary) in each of the patients studied over 24 weeks (Figures 7-9).

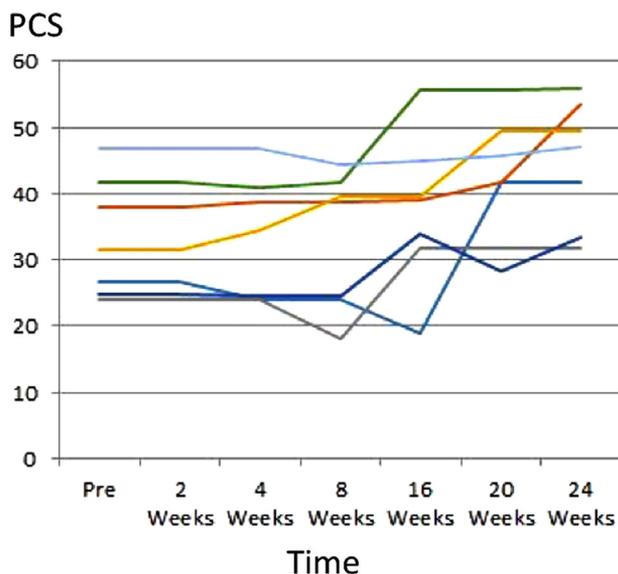


Fig. 8 – Graph demonstrating dynamics of physical component summary (PCS) scores, SF-36 over 24 weeks. (Color version of figure is available online.)

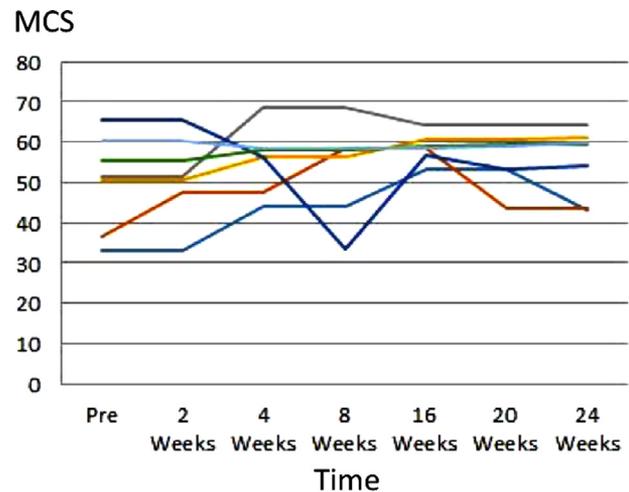


Fig. 9 – Graph demonstrating dynamics of mental component summary (MCS) scores, SF-36 over 24 weeks. (Color version of figure is available online.)

Discussion

IVD degeneration is a multifactorial process involving changes in disk composition, structure, and function. Such changes may include progressive loss of proteoglycans and water content in the nucleus pulposus, filling of the nucleus pulposus space with fibrocartilage, disruption of the annulus fibrosus, and osteophyte formation in adjacent vertebral bone. Also changes in the IVD cell population have been implicated as the cause of IVD degeneration. The repairing capacity of the IVD has been debated extensively over the years. The disk notochordal cells (NC), which are primarily responsible for producing cells of the nucleus pulposus of the IVD, are noted to diminish in time thus resulting in disk degeneration. It is unclear whether the NC die or differentiate into chondrocyte-like cells. Omlor et al⁴ have implicated several factors influencing the process such as high NC nutritional demands, high rates of NC apoptosis, and stimulation of chondrocyte migration from endplates.

The biochemical environmental changes occurring inside the disks leading to IVD are unknown. Some researches speculate a complex interactive phenomenon between growth factors, genes, and proteinases as the cause. Several growth factors have been discovered within disks and have been considered key factors in IVD metabolism and degeneration. Transforming growth factor beta (TGF- β) consists of a series of peptides has been associated with synthesis of collagen and proteoglycans thereby playing an important role in ECM accumulation.^{5,6} In addition, growth factors such as TGF- β 1 and TGF- β 2, basic fibroblast growth factor, and platelet-derived growth factor are noted to participate in cellular remodeling leading to structural changes associated with degeneration.⁷ In addition, other growth factors such as vascular endothelial growth factor A expressed in the normal hypoxic conditions of the mature disk plays an important role in NP survival due to cell migration, new blood vessel growth, and antiapoptosis of blood vessel cells.⁸ Hence, the IVD process is a complex interaction between various growth

Table 2 – Effects of the growth factors produced by platelets.⁹

PDGF	Macrophage activation angiogenesis fibroblast chemotaxis and proliferative activity collagen synthesis proliferation of bone cells
TGF- β	Enhances the proliferative activity of fibroblasts stimulates biosynthesis of type I collagen and fibronectin induces deposition of bone matrix inhibits osteoclast formation and bone resorption
IGF-I	Chemotactic for fibroblasts and stimulates protein synthesis enhances bone formation by proliferation and differentiation of osteoblasts
PDAF	Induces vascularization by stimulating vascular endothelial cells
PDEGF	Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts
PF-4	Stimulates the initial influx of neutrophils into wounds migration and mitosis of endothelial cells
EGF	Cellular proliferation differentiation of epithelial cells
VEGF	Migration and mitosis of endothelial cells angiogenesis creates blood vessel lumen and fenestrations chemotactic for macrophages and granulocytes vasodilation (indirectly by release of nitrous oxide)

EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; IGF-I, insulin-like growth factor 1; PDAF; PDEGF, platelet-derived epidermal growth factor; PDGF, platelet derived angiogenesis factor, PF-4, platelet factor-4.

factors and restoration of their balance is the key in preventing IVD process. Authors believe this would be an area of significant research in foreseeable future.

PRP has been clinically used in various specialties for its healing properties attributed to autologous growth factors. These factors in addition to their secretory proteins accelerate the healing process at the cellular level. Civinini et al⁹ described the growth factors present in PRP and their roles at cellular level noted below (Table 2).

In line with the mechanism of action noted above, we have noted clinical benefits in patients when injected with PRP into their nucleus pulposus. This is noted in patients at various points along the spectrum of disk degeneration starting from disk desiccation and disk bulge to annular tear and contained protrusion. We noted decrease in pain level and functional improvement in all our patients but could appreciate structural improvement in only 2 out of 6 patients. Larger well-designed clinical trials are needed to understand this phenomenon as well as the full effect of PRP on various types of disk pathology. In addition, the effect of age and extent of degeneration, presence or absence of nerve root compression, site and nature of disk damage on the treatment with PRP is still to be understood and needs further investigation. Several questions such as the most effective biochemical concentration of the PRP, frequency and number of intradiscal treatments for most optimal benefit, efficacy of PRP-impregnated scaffolds still remain unanswered and are being actively investigated.

The limitations associated with such therapies also need to be understood. The efficacy of intradiscal biologics rely on the presence of viable and functioning resident disk cells, which have been shown to decrease in during the progression of the IVD. Adult mesenchymal stem cells, capable of differentiating down the discogenic lineage have been considered by some as a suitable source for IVD tissue engineering. However, several questions such as ensuring correct lineage, providing adequate environment for cell sustainability and optimal functioning in degenerated disk still remain open for further investigation.

In conclusion, intradiscal PRP injection is an encouraging treatment in patients with discogenic chronic low back and leg pain. In the hands of skilled interventionist, this treatment appears to demonstrate good efficacy and safety profile. Although our preliminary results have been promising, further well-designed randomized controlled studies are warranted to understand the full breath of its efficacy, risks, applications, and complications.

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