

Case Series

Regenerative Injection Treatment in the Spine: Review and Case Series with Platelet Rich Plasma

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Abstract

Background: Platelet-Rich Plasma (PRP) has been used for a variety of musculoskeletal disorders including tendinopathies and Osteoarthritis. Few studies exist for PRP in the spine, except for studies involving disc pathology. However, numerous studies exist involving the use of Prolotherapy for spinal disorders. Both Prolotherapy and PRP can be considered within the broad category of Regenerative Injection Treatment (RIT), which are proposed to strengthen or repair injured ligaments, tendons, muscle, cartilage, and bone via injections of proliferative solutions, growth factors, or cells. Provided that double blind randomized controlled trials have shown both PRP and Prolotherapy to be effective in treating similar regions of the body, it is reasonable to consider that PRP could be comparatively effective as Prolotherapy in treating pain related to the facet joints, capsules and associated spinal ligaments.

Objective: Our aim is to provide an overview of Prolotherapy and PRP applications in the spine and present a 5 patient case series of PRP injections involving the lumbar, thoracic, and cervical spine.

Study design: This study is a single center observational case series with 5 patients. Patients were selected on the basis of a strict diagnostic criteria and inclusion factors. Each patient received a series of 3 PRP injections into the affected facet joints and surrounding ligaments using fluoroscopic or ultrasound guidance. Relative immobilization with bracing was prescribed for 72 hours following the injections. Follow up examinations ranged from 6-12 months.

Setting: Procedures were performed in an outpatient setting in Los Angeles, California.

Results: Case 1: 60% symptom improvement following 2nd injections, 100% improvement & return to sport at 6 months; Case 2: at least 30% symptom improvement following 1st injection, 60% improvement following the 2nd series, & 1/10 VAS scale at 9 months; Case 3: at least 40% symptom improvement following 2nd injections, 2/10 VAS scale and improvement in functional status at 12 months; Case 4: 70% symptom improvement & increased functional status following 3rd injections; Case 5: 65-70% symptom improvement and increased functional status at 6-month follow-up. Patient reported reduced fear and anxiety over inciting events, improved sleep, and decreased pain medication use.

Limitations: The self-reported VAS pain scale and functional scores could be a source of bias and potentially decrease the validity of the results. However, the cost effectiveness and subjectivity of such measurements make it an easy to use method for measuring therapeutic efficacy through patient satisfaction, regardless of objective measures. The small sample size is also a limitation, and larger patient sizes in future studies are needed to further evaluate the treatment's effectiveness. In addition, the follow up time ranged from 6-12 months. To better assess the long term effects of such treatment, patient follow up at 18 and 24 months would provide better long term data.

Conclusions: Platelet Rich Plasma injections can potentially represent a viable treatment option for spinal pain related to facet joints, capsules, and spinal ligaments. Further investigation with larger patient numbers and longer follow up periods are needed.

Introduction

Platelet-Rich Plasma (PRP) has been used for a variety of medical disorders since the late 1980s [1]. The majority of research and publications for PRP in orthopedics and sports medicine

have focused on tendon injuries [2] including patellar tendinosis (jumper's knee) [3], lateral epicondylitis (tennis elbow) [4] and Achilles tears/tendinopathy [5]. More recently, high quality studies including randomized controlled trials have emerged using PRP

for osteoarthritis [6,7]. There have been limited studies of PRP in the spine focused almost exclusively on disc pathology but none thus far outside of the operative setting for facet arthropathy, spondylolisthesis, radiculopathy or mechanical instability. There have been a number of studies, however, on prolotherapy for spinal disorders. Prolotherapy and PRP can be considered within the broad category of Regenerative Injection Treatment (RIT). The overall goal of RIT is to strengthen or repair injured or weakened musculoskeletal structures including ligaments, tendons, muscle, cartilage, and bone [8] via injections of proliferative solutions, growth factors or cells.

Our aim is to provide an overview of Prolotherapy and PRP applications in the spine and present a case series in which fluoroscopically or ultrasound-guided PRP injections were used to treat ligaments and facet joints of the lumbar and cervical spine in patients with non-radiating back or neck pain refractory to physical therapy, trigger point injections, medial branch blocks, or radio-frequency ablation. The diagnosis of facet-mediated pain was made via careful work-up to ensure elimination of alternative etiologies. Treatment outcomes were evaluated via patient questionnaires of VAS pain scale and percent return of function scores.

Low back pain

Low back pain (LBP) is one of the most common reasons patients visit their primary care physicians. More than 80% of Americans experience some form of LBP in their life; 15-20% develop prolonged pain and 4-8% experience chronic pain [9]. LBP is the second greatest cause of lost work time just behind the common cold. Anatomic sources of persistent low back pain include the lumbar intervertebral discs, facet (zygapophysial) joints and the sacroiliac joint [10-14]. Intervertebral disc disorders have been attributed to be the cause of persistent low back pain in up to 40% of patients [11-13]. Manchikanti et al. used anesthetic injections to diagnose patients with chronic low back pain and determined that the disc was the source of pain in 26% and the facet in 40% [13]. For patients whose pain did not fall into the category of discs, facet or sacroiliac joints, mechanical instability or biomechanical dysfunction of the spine secondary to ligamentous laxity was identified as the likely cause.

In cases of mechanical instability secondary to ligament laxity, joint hypermobility causes the vertebrae to undergo micro-movements, resulting in a compensatory increase in tone of surrounding paraspinal muscles [15,16]. Potentially as a result of excessive vertebral movement and increased paraspinal muscle tone, the spine may undergo changes including joint arthrosis and the development of myofascial pain. In attempting to use RIT to treat low back pain, it is imperative that the anatomical source of pain be defined as best as possible and that a rational treatment plan be formulated on the basis of the purported mechanisms of action for hyperosmolar dextrose solution or PRP.

Prolotherapy

Contemporary Prolotherapy consists of a hyperosmolar dextrose solution injected into a weak painful region or joint at the fibro-osseous junctions of fascia, ligaments and tendons in order to stimulate an inflammatory reaction [17]. Prolotherapy depends on the provocation of a pro-inflammatory state that recruits growth factors and stimulates the natural healing cascade. The pro-inflammatory state is induced at the site of injection via the hyperosmolar dextrose

solution, which is hypothesized to promote cellular dehydration, lysis and release of cellular fragments. The cellular fragments are thought to initiate the migration of granulocytes and macrophages and promote tissue healing [17]. The hyperosmolar solution itself has also been shown to recruit growth factors and other healing properties to the injection site [18-20].

Positive results for Prolotherapy have been published for a variety of conditions including lateral epicondylitis [21], osteoarthritis [22], sacroiliac joint pain [23], chondromalacia patellae [24], fibromyalgia [25], chronic groin pain [26] and Osgood-Schlatter disease [27]. Prolotherapy has also been studied for sub acute and chronic low back and neck pain [18,28-33], but is still considered to be experimental because of mixed outcomes in several studies and only one double blind randomized controlled trial showing improvement relative to placebo [33].

The theory that dextrose-induced inflammation and tissue proliferation could lead to stronger more resilient connective tissue is supported by findings of increased ligament size and density on electron micrography [34] and positive preliminary results in cases of Anterior Cruciate Ligament (ACL) laxity [35,36], sacroiliac joint [31] and knee instability secondary to medial and lateral collateral ligament laxity [37]. Typically, 4-8 injections are performed at a time and repeated several times 1.5-3 weeks apart. These have traditionally not been image-guided but are being done increasingly frequently with ultrasound-guidance for greater precision and accuracy [38].

Platelet rich plasma

Platelet Rich Plasma (PRP) consists of a concentrate of platelets and growth factors extracted from the patient's blood and injected to the site of injury or pathology. PRP treatment is considered part of an evolving area of medicine referred to as "Orthobiologics" and defined as autologous cellular therapies which exhibit regenerative potential and can promote and accelerate healing in a wide range of musculoskeletal injuries including bone and soft tissue [39,40]. PRP is typically derived by centrifugation from whole blood. While autologous whole blood has also been found to be effective for lateral epicondylitis [41], medial epicondylitis [42] and Achilles tendinopathy [43], PRP is widely considered to be superior. For purposes of this paper, further discussion about autologous blood products will be devoted to PRP.

PRP is formed by concentrating platelets from a patient's whole blood through centrifugation, usually to a minimum of 4 times above baseline levels [44]. However, recently several classification systems for PRP have started to emerge, incorporating not just platelet concentration, but also leukocytes, red blood cells, and exogenous activation [45]. The Alpha Granules within the platelets contain a myriad of growth factors including Platelet-Derived Growth Factor (PDGF), transforming growth factor- β (TGF- β), Insulin-Like Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor (EGF), which have been shown to play important roles in the healing cascade [38,45,46]. It is theorized that the direct injection of PRP with its concentrated mixture of growth factors and cytokines into the site of pathology initiates both an immediate and delayed inflammatory response. Similar to Prolotherapy, PRP has been shown to initiate strengthening and restoration of connective tissue during the initiated healing

response [47-49] and thus hypothesized to potentially strengthen the composition of ligament fibers and decrease ligament laxity.

PRP has been found to exhibit significant regenerative potential in a variety of medical fields including wound healing, dentistry, cosmetic and cardiothoracic surgery [50]. Its application in musculoskeletal injuries including tendinopathies [2,4] and osteoarthritis [7,46,50] has occurred relatively more recently but has experienced rapid growth. Among musculoskeletal specialists, PRP has become an exciting topic of discussion and emerging research [51]. PRP injections can be targeted directly to the site of pathology and performed in an outpatient clinic or surgery center. Typically a series of 1-3 injections are performed in one visit, ideally with image guidance and repeated 4-6 weeks apart depending on the diagnosis, patient tolerability and response.

Applications of prolotherapy in the spine

Prior to a discussion of applications in the spine, it is important to understand some key points in the history of Prolotherapy and its progression towards becoming a viable treatment option. Several landmark studies in the timeline of Prolotherapy research contributed largely to its credibility and acceptance. In 1983 Liu et al. performed a double-blind study of sodium morrhuate solution versus saline in rabbit medial collateral ligaments and found evidence of increased ligament mass and thickness on electron microscopy, confirming its hypothesized mechanism of action in the treatment of musculoskeletal and soft tissue injuries [34]. In 1987, Ongley et al. performed a double-blind study of dextrose-glycerine-phenol versus saline injections in 81 subjects with chronic low back pain and found improvements in disability of 50% in the experimental group and 16% in the control group [52]. In 2005, the Mayo Clinic featured Prolotherapy in its Health Letter publication as an alternative treatment for chronic pain, stating "Prolotherapy stimulates tissue growth and can potentially be used for tendon and ligament pain" [53]. These papers and others helped Prolotherapy emerge as a rational treatment for chronic low back pain deserving of further attention and research.

Facet joints and ligaments: There have been a number of studies of Prolotherapy injections to the ligaments and joints of the spine [18,33,54]. Dagenais et al., in a review of 26 observational cohorts and 5 randomized clinical trials, concluded that there has been a significant degree of variability in treatment methods and solutions among various studies for back pain (n=22), neck pain (n=3), cervical headaches (n=3) and thoracic pain (n=3) [18].

Ongley et al. published data on eighty-one patients with low back pain with a history of failed response to exercise bracing and/or medication. Subjects were randomly assigned to receive six weekly injections of either lidocaine with dextrose-glycerine-phenol solution or lidocaine and saline to the lumbosacral fascia, posterior sacroiliac and interspinous ligaments and capsules of the lumbar facet joints [52,55]. Outcomes were assessed via subjective assessments of pain and disability obtained from the Roland and Waddell disability indexes and objective assessments of spinal range of motion, symmetry and tenderness 6 months following the last in the series of injections. At the completion of the study, 88% (35/40) of the proliferant group and 40% (16/41) of the control group achieved a 50% or greater diminution in pain or disability scores.

The main confounding factor of the Ongley et al. study is the understanding that control injections of saline and lidocaine were not inert and are capable of exerting a therapeutic effect via similar mechanisms although less effectively as Prolotherapy solution, namely the induction of inflammation and tissue repair based on mechanical irritation and recruitment of growth factors [56-59]. The potential healing effects and pain reduction exhibited in the control group likely narrowed the difference in outcomes statistical significance of the Prolotherapy effect. A second confounding factor could have been the injection of phenol, which has a neurolytic effect and likely reduced pain by providing prolonged anesthesia to nerve fibers communicating pain from sensitized structures. The potential therapeutic effect of control injections might explain why sclerosing injections were found to be ineffective in the study by Dechow et al. [54]. Other potential reasons for negative results in Prolotherapy trials include lack of identification of a specific pain generator or the possibility that disc-mediated pain, with a prevalence of up to 40% in the adult population, was the cause of pain.

Intervertebral discs: In contrast to the abundance of Prolotherapy research for connective tissue dysfunction and facet mediated pain of the spine, Prolotherapy for disc mediated pain is not as well studied, likely attributed to the more technically advanced procedure techniques required to access the disc. In a unique study, Miller and Reeves performed hypertonic dextrose solution injections into the chronic, advanced degenerative discs. Patients were followed for a mean of 18 months and grouped according to responses, with 43.4% (33/76) exhibiting sustained average improvements in VAS score from 9/10 to 2/10 at final follow up [57].

Applications of PRP in the spine

Intervertebral discs: In contrast to Prolotherapy, PRP studies in the spine outside the operative setting have almost exclusively focused on disc pathology, using in-vitro and animal models for which there have been promising results justifying further exploration into its future utility as a viable pain management procedure [58-65].

Sawamura et al. studied PRP application via impregnated hydrogel, into the nuclei of traumatically induced degenerated discs in rabbits and discovered increased expression of mRNA proteoglycan core protein and type II collagen as well as reduction of apoptotic cells when compared to placebo treatment. At the completion of the study, MRI revealed better preservation of disc water content and height in PRP treated discs [59]. Chen et al. cultured human intervertebral disc cells together with PRP introduced with a novel intervertebral disc organ culture system resulting in significantly increased levels of mRNAs involved in chondrogenesis and matrix accumulation [65]. Pirvu et al. reported similar findings in an in vitro study analyzing PRP and Platelet Lysate effects on bovine Annulus Fibrosus (AF) cells. The study cultured AF cells in different concentrations, 25% or 50%, of PRP or Platelet Lysate, and showed increased production of GAG (highest in the 50% Platelet Lysate group) as well as increased matrix synthesis [64]. Another recent in vitro study by Kim et al., investigated the anti-inflammatory effect of PRP with collagen matrix on human nucleus pulposus cells in response to pro-inflammatory cytokines (TNF- α and IL-1) [61]. The study illustrated that PRP added to the collagen matrix suppressed cytokine-induced pro-inflammatory degrading enzymes and mediators in the nucleus

pulposus cells. The study also showed that the addition of PRP rescued gene expression concerning matrix synthesis, thereby stabilizing NP cell differentiation.

Nagae et al. injected PRP impregnated gelatin microspheres into the nucleus pulposus of rabbits with subsequent findings of new proteoglycan synthesis [58]. Gullung et al. performed a randomized controlled trial to analyze the early and late effects of PRP injections in rats. Degenerative disc changes were induced via the percutaneous needle puncture technique with injection of PRP immediately post-injury, at 2 weeks post-injury, or not at all. The PRP-treated groups retained more normal morphologic features, had fewer inflammatory cells and higher fluid content on MRI, with the effects more pronounced in the immediate treatment group [62]. Although animal and in vitro studies indicate that PRP could serve as a potential therapeutic option for disc degeneration, the exact pathologic mechanism of disc degeneration is still unknown [65].

Research for human intra-disc PRP injections in a non-operative setting has started to emerge, although trials are limited at this point [51,66,67]. Akeda et al. injected PRP into the discs of 6 patients with chronic low back and DDD in one or more lumbar segments. VAS scores improved from 7.1 ± 1.2 to 1.8 ± 2.0 , $p < 0.01$ and RDQ scores from 11 ± 1.8 to 3.2 ± 2.4 , $p < 0.01$ with results sustained over 6 months [66]. The authors have previously described an intradiscal PRP injection technique and results in 5 cases of lumbar and thoracic disc-mediated pain in the textbook *Platelet-Rich Plasma: Regenerative Medicine: Sports Medicine, Orthopedic, and Recovery of Musculoskeletal Injuries* [51]. The 5 case examples were selected among a series of 35 patients and 47 discs with chronic disc pain who had failed physical therapy, epidural and facet injections and the passage of at least 6 months of time. The diagnosis was confirmed on the basis of complete resolution of pain with anesthetic discography. Bodor et al. reported a positive response to intra-discal PRP in approximately 2/3rds of patients, half of which had “excellent” and half “good” results on the basis of pain resolution and ability to return to activities of daily living and exercise without pain or regular use of any medications. The effects were sustained at 6-12 months following a single injection per disc [51].

Radiculopathy: The majority of classic lumbar radiculopathies are attributed to herniated discs rather than actual neural foraminal narrowing secondary to lumbar spondylosis. However, annular disc tears can also cause a chemical radiculopathy from leakage of inflammatory mediators into the epidural space [68,69]. Whether attributed to mechanical or chemical etiology, research for the application of PRP treatment of radiculopathy is completely uncharted territory at this time. Conventional treatment options are not ideal given lack of long-term results with current interventional strategies and notoriously unpredictable short and long-term surgical outcomes after laminectomies and microdiscectomies. Extensive review of the literature deemed epidural steroid injections apt at providing moderate short-term symptom relief, based on a fair amount of evidence [70]. There is scarce evidence supporting less commonly performed non-surgical treatments for lumbar radiculopathy including pulsed radiofrequency to the dorsal root ganglion [71] or percutaneous coablation nucleoplasty [72].

Many patients with acute radiculopathy opt for surgery after failing

a round of physical therapy and a series of epidurals. Interestingly, evidence points to better short-term relief of leg pain post-operatively for those undergoing surgery earlier in the development of sciatica as compared to prolonged conservative care. However, at 1 and 2 year follow-ups, no significant differences were found between surgery and traditional non-operative care [73]. Alternative non-invasive treatment options for patients with chronic radiculopathy also include traction or inversion tables, chiropractic manipulation and acupuncture. Based on limited efficacy and difference in outcomes of available treatments, it is not surprising that more patients and physicians alike are considering complimentary methods such as RIT. A Cochrane review reported two non-controlled studies that showed statistically significant differences in favor of Prolotherapy in treatment of chronic low back pain, with participants showing more than 50% reduction in pain scores from baseline at 6-month follow-up [54]. There are no articles to date reporting on the treatment of chronic radiculopathy with epidural PRP.

An explanation of PRP's potential role in neural repair is warranted at this time in order to justify further discussion of this treatment for radiculopathy, a nerve-mediated symptom generator. The healing potential of Platelet-rich plasma is attributed in part to its growth factors including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor- $\beta 1$ (TGF- $\beta 1$), Insulin-Like Growth Factor (IGF), and Vascular Endothelial Growth Factor (VEGF). These growth factors are associated with repair processes of the central nervous system. Takeuchi et al. conducted a study related to PRP's impact on development of axonal growth in spinal cord tissues [74]. In particular, these findings imply that IGF-1 and VEGF enhance axon growth of the spinal cord and TGF- $\beta 1$ hinders such growth. Future autologous therapies will likely be customized to eliminate unwanted pro-inflammatory cytokines for particular regions like the spine. Results of axon growth in co cultures illustrated dependence on the environment of the spinal cord, causing researchers to hypothesize that the growth factors in PRP may have a much greater impact on the spinal cord in vivo. In addition, peripheral nerve regeneration may be stimulated by the same growth factors found in PRP given that they have important roles in extracellular matrix regeneration. A few case studies exist for peripheral mononeuropathies. Anjayani et al. found that perineural PRP injection around the peripheral nerves of leprosy patients with peripheral neuropathy had a positive effect on sensory function at two weeks post-injection [75]. In addition, a single patient case study by Doss et al. demonstrated efficacy of ultrasound-guided PRP to the distal branches of the trigeminal nerve in a patient with Trigeminal Neuralgia, suggesting that PRP played a role in myelination and potentially modulated neuronal activity [76].

At the spine division of the primary authors' physical medicine and rehabilitation clinic, an abundance of patients with radiculopathy seek alternative non-surgical treatments after failing traditional conservative measures. These include those who may have already had surgery with ongoing or recurrent symptoms occurring immediately after surgery or within 12-24 months of the operation who may or may not have MRI findings of scar tissue or re-herniation of disc. Thirty of these patients received epidural PRP via the caudal or lumbar transforaminal route, 10 of which also received Traumeel, Sarapin and 5-10% dextrose along with the PRP.

Approximately one third of these patients only had improvement of pain for a few hours or the duration of effect of 0.5-1.0 cc lidocaine 0.5% injected into the epidural space at the time of the PRP injection, while one third had temporary relief anywhere from 6 weeks to 6 months and one third experienced long-lasting relief for 8 months or greater. Among the latter, approximately 1/3rd underwent 2nd and 3rd PRP epidurals. Various tabletop PRP systems were used for these epidurals with volumes ranging from 2-3 cc of PRP into the foramen to 6-8 cc into the caudal canal. There were no complications or increases in pain as typically occurs after PRP is injected into tendons or joints.

Facets joints and ligaments: Currently there are no published studies evaluating PRP injections into the connective tissues and articulating joints of the spine in humans or animals. Tolbert et al. described a 3 patient case series in which an integrative treatment approach was used along with ultrasound-guided hypertonic dextrose and platelet rich plasma injections to the facet joint capsules, the sacroiliac ligaments and joint and the caudal epidural space [77]. As previously mentioned, facet joints have been implicated in up to 40% of spine pain, especially in cases of spondylolisthesis and instability [13]. Given encouraging results in recent randomized trials for PRP for joints and tendons, it is logical to assume that PRP could be similarly effective in treating the facet joints, capsules and associated ligaments of the spine. The following is a series of patients with facet-mediated pain treated with PRP.

Methods

Patients were selected on the basis of history, physical examination, lack of significant disc pathology on MRI including herniated discs, annular disc tears or more than a moderate degree of degenerative disc disease. Patients must have failed the following: physical therapy, analgesics and trigger point injections. In addition, all lumbar patients must have failed lumbar medial branch radiofrequency neurotomies following successful resolution of pain with anesthetic medial branch blocks.

Platelet Rich Plasma was derived from patient's peripheral blood via a double-spin centrifugation method. For each patient, the PRP conformed to the following classifications: Platelet count > 1,500,000; no leukocytes; no red blood cells; and non-activated by exogenous means.

PRP was injected into the facet joints, capsules, supraspinous and interspinous ligaments using fluoroscopic or ultrasound guidance [78]. Thoracic spine injections also included the costovertebral joints, while lumbar spine injections also included the sacroiliac and iliolumbar ligaments. Relative immobilization was prescribed for 72 hours following the injections using a soft cervical collar, thoracic postural brace, or lumbosacral corset.

Outcome measures included Brittberg-Peterson Visual Analogue Scale (VAS), and a patient survey that included symptom relief and functional improvements.

Case Series

Case 1

28 y/o male Olympic pole-vaulter presented with one year history of mid-lower centralized neck pain and weakness with slight spread

into the right upper peri-scapular region rated at 6/10 overall on the pain scale. The only way he could relieve his pain was by lying down and resting supine. Aggravating factors included neck flexion followed by extension and any right arm overhead activities. He had failed numerous conservative and interventional treatments including physical therapy, massage, chiropractic, mechanical spine decompression, hyperbaric oxygen treatment, acupuncture, myofascial trigger point injections, epidural spine injections and C6 and C7 medial branch radiofrequency neurotomies.

On physical exam there was tenderness to palpation of the right greater than left C5, C6 and C7 facet joints and mild crepitus at the T1 and T2 costo-vertebral joints during active cervical flexion and extension and right scapular rotation. Cervical spine range of motion was normal but there was pain at end range side bending to the right and lateral rotation. MRI of the cervical spine revealed mild cervical facet arthropathy bilaterally at C5-6 and C6-7 and multi-level mild disc bulges up to 1-2 mm with no evidence of stenosis or nerve compression.

The patient received 3 PRP injection treatments one month apart with 1 ml of PRP injected to the posterior aspect of the bilateral C5-6, C6-7 and C7-T1 joint and corresponding posterior spinal ligaments using ultrasound guidance. After the second in the series of injections, the patient expressed noticeable symptom relief of at least 60%. At 6-month follow-up, the patient reported complete pain relief with unrestricted return to training and competition in pole-vault and normalization of physical examination findings except for some minor residual restriction in right scapular mobility.

Case 2

55 y/o man with a 15-year history of progressively worsening chronic low back pain with intermittent severe exacerbations and locking lasting several days. He reported a baseline 6/10 pain level with exacerbations to 9/10. He had failed analgesic medications, extensive physical therapy, lumbar bracing, osteopathic manipulations, inversion and lumbar traction, myofascial trigger point injections, and bilateral L3-4, L4-5, L5-S1 medial branch blocks and radiofrequency denervation.

On physical examination, he had pain and restriction of lumbar extension and rotation and tenderness to palpation of the quadratus lumborum and paraspinous muscles from L4 through S1. MRI of the lumbar spine showed mild-moderate bilateral L4-5 and L5-S1 facet arthropathy, grade I L4-5 anterolisthesis and a 2 mm L5-S1 central disc bulge.

The diagnosis of facet-mediated pain was made on the basis of the history, physical examination and imaging studies and the patient underwent a series of 3 ultrasound-guided PRP injections treatments at 5-6 week intervals to the bilateral L4-L5 and L5-S1 facet joint capsules, corresponding posterior spinal and sacroiliac ligaments, including the iliolumbar ligaments. Following the first series of injections, the patient reported symptom relief of at least 30% and with improvement to 60% after the second series. At 9 months follow-up, the patient reported that his pain level was at 1/10 with no acute flare-ups since the first series of PRP injections. On physical examination, the lumbar paraspinous muscles were non-tender and with pain-free lumbar extension and rotation.

Case 3

67 y/o man with history of congenital and degenerative scoliosis of the lower thoracic and upper lumbar spine presented with constant 4/10-6/10 debilitating localized ache in his left lower posterior rib and upper lumbar regions that began insidiously several years prior. Pain was exacerbated by prolonged standing and sitting, and partially relieved with lying supine, therapeutic massage, and Lidoderm patches. The patient had many failed treatments including: medications such as muscle relaxants and anti-inflammatories, physical therapy, myofascial trigger point injections and upper lumbar medial branch blocks.

On physical examination, there was moderate levoscoliosis at T10-L3 with extreme restriction along with pain provocation for lumbar extension and bilateral side bending. There was tenderness to palpation of the left lower thoracic and upper lumbar joints; spasm and myofascial trigger points in the quadratus lumborum. MRI of the thoracic and lumbar spine showed 19-degree levoscoliosis with the apex at L1 and moderate to severe L1-2 and L2-3 facet arthropathy.

The diagnosis of facet-mediated pain was made on the basis of the history, physical examination and imaging studies and the patient underwent a series of 3 PRP injection treatments at 4 week intervals into the left T10-L3 facet capsules, corresponding posterior spinal ligaments, and left paraspinal muscles. After the second series of injections, he reported pain relief of at least 40%. At the 12-month follow-up visit, his pain was at 2/10 with significant improvement in functional status. Physical exam revealed similar structural abnormalities to the original exam except for significant reduction in muscle tender points and tone.

Case 4

52 year old otherwise healthy male presented with a 10 year history of chronic progressively worsening low back, morning stiffness, pain and stiffness with rising from sitting, prolonged standing and playing golf. He had tried tramadol and baclofen, physical therapy, chiropractic, trigger point injections into the paraspinal muscles, acupuncture and therapeutic massage. He experienced significant but short duration (4-6 weeks) relief following bilateral intra-articular L3-4, L4-5 and L5-S1 facet corticosteroid injections, performed three times within a year. He ultimately underwent bilateral L2, L3, L4 and L5 medial branch radiofrequency neurotomies which provided only 4-5 months of relief and did not relieve his symptoms as much as the corticosteroid injections.

On physical exam, there was pain and restriction with lumbar extension, reproducible pain with back extension from a prone position, mild tenderness to palpation over the lower lumbar facets and flattening of the normal lumbar lordosis during standing. MRI showed moderate hypertrophic facet arthropathy and mild disc bulging and associated neural foraminal and central canal stenosis at L3-4, L4-5 and L5-S1.

The diagnosis of facet-mediated pain was made on the basis of the history, physical examination and imaging studies and the patient underwent a series of 3 fluoroscopy-guided PRP injections at 6-8 weeks intervals into the bilateral L4-5 and L5-S1 facet joints and overlying paraspinal muscles, sacroiliac joints and iliolumbar ligaments.

Following completion of the series of injections, he reported a 70% reduction in all symptoms and improvement of activities of daily living and golf.

Case 5

71 year old woman with chronic widespread osteoarthritis presented with chronic neck pain, stiffness, reduced mobility and ability to perform activities of daily living. She has had neck and suboccipital pain for 40 years with marked progression of pain and disability since a rough safari ride in Africa. She tried methocarbamol, tramadol, hydrocodone, meloxicam and diclofenac as well as extensive physical therapy, osteopathy and acupuncture. She underwent fluoroscopically guided cervical facet and epidural corticosteroid injections, positive medial branch blocks and an unsuccessful radiofrequency neurotomy.

On physical exam, there was approximately 75% reduction of cervical spine range of motion in all planes. There was tenderness to palpation of the bilateral C2-3 through C6-7 facet joints. MRI revealed severe cervical spondylosis with moderate to severe facet arthropathy from C2-3 through C6-7, degenerative disc disease and associated mild sub-clinical foraminal stenosis at multiple levels.

She underwent two independent surgical consultations and was determined not to be a good surgical candidate. She then received a series of 3 ultrasound-guided PRP injections 4-6 weeks apart to the bilateral C2-3, C3-4, C4-5, C5-6 and C6-7 facet capsules, supraspinous and interspinous ligaments, following which she experienced substantial flare-ups of her pain lasting 7-10 days and requiring hydrocodone to avoid reactive cervicogenic headaches.

At 6-month follow-up from her last series of PRP injections, she reported 65-70% improvement in pain. Physical examination revealed approximately 50% improvement in lateral rotation and side bending bilaterally, as well 50-75% improvement for cervical extension. She reported reduced fear and anxiety regarding long bumpy car rides and eliminated the use of a soft cervical collar for sleep. She reported requiring only naproxen for pain as needed.

Discussion

Regenerative Injection Treatment (RIT), such as Prolotherapy, autologous whole blood or PRP, is becoming an increasingly popular alternative in the treatment of musculoskeletal disorders related to connective tissue dysfunction and joint pathology. For years, interventional spine specialists and surgeons have focused on specific etiologies for low back pain ranging from facet joints to nerve roots to discs and vertebrae. As is often the case, a single anatomical factor (facet or disc or nerve root) is not found to be the source of pain but rather a cluster of factors. A fundamental tenet of Prolotherapy is that ligament laxity as a result of injury, aging and or loss of segmental height results in micro-instability and pain. The natural response to micro-instability is reactive bone growth in the form of osteophytes, facet hypertrophy, and spondylosis. In contrast to traditional treatments that treat pain pathways, RIT attempts to facilitate and accelerate the natural healing response by strengthening ligaments and healing tears in avascular areas, such as the intervertebral disc, by mediating various biologic cytokines.

Double blind randomized controlled trials have shown both PRP

and Prolotherapy to be effective in treating varying regions of the body [21,27,79,80]. It is therefore reasonable to consider that PRP could be similarly effective in treating pain related to the facet joints, capsules and associated spinal ligaments. These limited case examples provide preliminary experience in treating these areas and will fuel the desire for further research. At the very least, PRP is autologous and has limited side effects other than a temporary increase in pain.

Future directions for RIT in the spine involve Bone Marrow Concentrate (BMC) with its potent mix of Mesenchymal Stem Cells (MSCs). Several in-vitro and animal BMC studies have shown positive results [81,82], while several intra-discal BMC trials in humans have presented mixed results thus far [83-85]. In the Haufe and Mork trial there was no benefit in 10 patients at 1 year with most electing to have surgery [83]. In the Orozco et al. study 9 out of 10 experienced significant improvements of pain, function and water content on T2 weighted MRI [84]. In Yoshikawa et al., 2 patients experienced significant pain relief sustained at 2 years follow-up [85].

Research investigating the application of BMC for epidural or facet joint and ligament injections does not exist at this time but is likely to occur in the near future given its ease of use, strong safety profile and increased applications for osteoarthritis of the hip and knee [39,44] Further controlled trials on biologic based therapies for the spine are needed to address the large void between the standard conservative care & surgical intervention.

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