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Research Article

A Regenerative Interventional Approach to the Management of Degenerative Low Back Pain

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Abstract

Objective: Low back pain has been strongly related to the degenerative process of the spine, especially the degeneration of the intervertebral disc and facet joints. The main procedures for the management of low back pain are not intended to slow down or reverse the degenerative process. Platelet Rich Plasma (PRP), an orthobiologic product, has been the subject of several studies in the management of low back pain.

Methods: A prospective case series study presenting the clinical results of 23 patients treated with PRP injections performed following clinical a interventionist protocol called PerMuTIS - Personalized Multi Target Biologic Injection of the Spine. The method to obtain the platelet concentrate was the Simple Double Spin technique, a low-cost double spin that produces Leucocyte Rich PRP. Baseline scores of pain and disability using the Visual Analog Scale (VAS) and Roland-Morris Disability Questionnaire (RMDQ) were recorded.

Results: Mean VAS pain score across the cohort decreased by approximately 62%, while the Roland-Morris disability score decreased by about 60% at 52 weeks. There was no report of adverse events. The Leucocyte and Monocyte Rich PRP product showed concentration of 4.3X above baseline, with monocytes concentration of 3.2X baseline.

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Conclusion: The concept of application in multiple targets using a simple and low-cost preparation technique proved to be feasible and without reports of serious side effects that compromise its indication. The PerMuTIS - Personalized Multi Target Biologic Injection in the Spine Technique using Simple Double Spin protocol demonstrated safety and feasibility in this prospective study of patients with low back pain who failed conservative treatments. Large scale, multicenter randomized clinical trial will provide an appropriate level of evidence to assist in clinical practice.

Keywords

Degenerative Disc Disease; Facet Joint Pain; Low Back Pain; Platelet-Rich Plasma; Spine Injection; Orthobiologics; Regenerative Medicine

Introduction

Currently, musculoskeletal diseases are the main cause of disability and health expenses, and their cost is greater than the treatment of cancer, cardiovascular diseases, and diabetes [1]. Among the most frequent musculoskeletal diseases, Low Back Pain is the most common, being ahead of cervical pain and knee arthrosis [2]. Low back pain is the leading diagnosis in Year Lived with Disability (YLD) and has an annual prevalence point of 18% in the general population [3]. In Brazil, the annual prevalence of Low Back Pain can reach more than 50% in the adult population [4]. Low back pain has a high economic cost with direct expenses and lost productivity and is one of the main causes of early retirement [5].

Low back pain has been strongly related to the degenerative process of the spine, especially the degeneration of the intervertebral disc and facet joints (facet arthritis) [6,7]. Due to its structural and biomechanical complexity, Degenerative Disease of the lumbar spine can manifest itself in different ways, and result in different clinical conditions. There are four main alterations found, which can manifest alone or in association: a) Discogenic Low Back Pain; b) Muscle Atrophy; c) Facet arthropathy and d) Disc Herniation.

Discogenic Low Back Pain is one of the most common causes of low back pain. Studies have revealed that the painful disc, without hernia, presents internal ruptures and areas with vascularized and granulation tissue, with extensive innervation within it [8]. Due to the avascular nature of the intervertebral disc, these findings are considered to be the result of a failed attempt at healing the disc. In some cases, the image diagnosis can be made through the Magnetic Resonance Imaging, where a disc with loss of signal on T2 is visualized (dehydration) and with a small focus of hypersignal in the posterior region, configuring an internal rupture, this injury is also called HIZ-Hyper Intensity Zone. However, this finding occurs in few patients. In the vast majority of cases, we only see initial degenerative changes, Pfirrmann grade II or III [9]. Modic type I alterations have also been shown to correlate with

positive discography [10]. The use of provocative discography can be useful, although in clinical practice it is an invasive procedure, of greater complexity and not free of complications, therefore it should be reserved for selected patients, preferably those who are already candidates for a surgical procedure [11]. There are several treatment proposals for discogenic low back pain currently. Nonsurgical management is the most important first-line option. If conservative measures fail, intradiscal techniques such as thermoablation or orthobiologics injection may be a good option. Major surgical procedures, such as lumbar fusion (arthrodesis), should be reserved as a second option in case other less invasive techniques fail [12].

The paraspinal muscles (multifidus, erector spinae, and psoas major) play a crucial role in lumbar spine stability. Muscle atrophy and fatty degeneration are common findings in patients with chronic low back pain [13]. Huang, et al., in a study involving degeneration models in rats, with imaging studies and histochemical analysis, demonstrated this relationship. In this study, disc degeneration was induced in guinea pigs, which after this event showed atrophy and fatty infiltration of the spinal muscles. He also performed a parallel analysis in humans with discogenic Low Back Pain, through MRI images. After analyzing the two groups, it was concluded that there is a causal relationship between fatty infiltration of the musculature and discogenic pain [14].

Facet pain is also one of the most common complaints of patients with low back pain. Facet joints are diarthrodial joints, with joint capsule and synovial membrane, while the surfaces are covered by cartilage. Its function is to assist in load transfer, to stabilize the spinal unit in flexion and extension, and to limit axial rotation [15]. Its oblique orientation contributes to resisting shear forces and limiting rotation. In a normal functional unit, compressive loads are absorbed mainly by the intervertebral disc (about 80%). In the degenerative process, with disc dehydration, there is a decrease in the internal pressure of the disc, and it ends up losing its ability to distribute and dissipate the compressive loads imposed on the spine. Pollintine, et al., demonstrated that in a degenerated disc, axial compression is not adequately absorbed by the disc, and this load is then transmitted to the facets, which can undergo an increase of 4 to 8 times their original mechanical demand. This increased load, associated with greater instability, results in joint injuries and the beginning of their degenerative process [16].

Next to disc degeneration, facet arthropathy is one of the main causes of low back pain. The main procedures for the management of low back pain of facet origin are injections with anesthetics and/or corticoids and thermal ablation of the capsular nerves, also known as the middle branch [17]. None of them are intended to slow down or reverse the degenerative process.

Disc Herniation occurs when the disc becomes dehydrated and loses the ability to absorb and dissipate compressive loads. It is more prone to internal fissures, which progress to complete ruptures, allowing disc material to leak into the spinal canal, resulting in a herniated disc. Herniated contents can cause symptoms through two mechanisms: direct mechanical compression of the nervous tissue, or through the inflammatory reaction resulting from the release of several cytokines, especially TNF Alpha and IL-6. So today we know that radicular

pain, or radiculopathy, can be result of mechanical compression and/or an inflammatory reaction, both caused by herniated disc material [18].

Considering that such techniques only treat the consequence of the degenerative process and do not interfere in its evolution, there has been a search for solutions that, in fact, modify the course of the disease. The search for therapies that control degenerative disease has increased, and several approaches have been proposed. A class of products known as Orthobiologics has gained space in research and clinical practice. These products take advantage of the repair and regeneration potential present in the body's native cells, redirecting their use for accelerated healing in degenerative orthopedic injuries or diseases. Derived from cells or substances found naturally in the human body, they improve the natural healing process or tissue regeneration, such as muscles, tendons and cartilage. Platelet-rich plasma and bone marrow aspirate are the most common examples of orthobiologics. They can fill the gap between the diagnosis of degenerative joint disease and the performance of major surgeries, such as prostheses, for example [19].

The attractive proposal of a low-cost biological therapy that stimulates tissue healing and regeneration has given space to several studies using autologous platelet concentrates, known as Platelet Rich Plasma (PRP). Platelets play a fundamental role in the entire tissue repair process, from hemostasis and blood clotting. Inside it are numerous proteins that are secreted in traumatic events, whose function is to assist in the repair of tissue damage. During tissue trauma, the platelet is activated and releases from its interior several tissue growth and regeneration factors. Dozens of signaling cytokines have already been identified, such as PDGF (Platelet-Derived Growth Factor), TGF (Transforming Growth Factor), VEGF (Vascular Endothelial Growth Factor), IGF (Insulin-like Growth Factor) and EGF (Epidermal Growth Factor). These factors are involved in tissue repair and healing, in all its phases, from hemostasis, inflammation, proliferation and remodeling. The actions of these factors range from the paracrine effect on local cells, to signaling to attract distant mesenchymal cells and stimulating cell differentiation into chondrocytes, osteoblasts or myocytes. Platelet-rich plasma is obtained from the individual's own peripheral blood, which, after collection, is subjected to a centrifugation process to separate the blood elements. The separation is based on the physical concept of differential centrifugation, where each component will undergo sedimentation according to its specific weight, dividing the blood into different layers. The heavier red blood cells will form the deepest layer. The white series cells will form the buffy coat and just above it will be the region where the highest concentration of platelets will be found. But superficially we will have pure plasma, or poor plasma, with sparse non-sedimented components. After centrifugation, the portion of the plasma where most of the platelets are found is collected, and this is then injected into the region of interest. The techniques and protocols for obtaining the concentrate vary from author to author, and there is still no consensus on the best technique. The advantage of being a simple, safe and low-cost procedure has resulted in several studies on its regenerative effect on skeletal muscle tissues [20].

There is still no consensus on the best management of patients with low back pain. Conservative measures such as physical therapy and analgesic medications do not interfere

with the degenerative process and cannot be considered as disease modifiers. Surgical procedures do not restore the degenerate structures, have a high rate of short- and long-term complications, and result in more disability than recovery. Recently, the use of autologous products, such as Plasma Rich in Platelets and Cell Concentrates, has been proposed as an alternative to a surgical approach in the management of patients with symptomatic degenerative disease of the lumbar spine.

A study previously published by our group showed good results in a protocol for the management of lumbar degenerative disease with the use of PRP in multiple painful structures of the lumbar spine, presenting the Multi Target concept [21]. The acronym PerMuTIS (Personalized Multi Target Biologic Injection in the Spine) was created to describe a concept of concurrent treatment of multiple pain generators in patients with LBP. We improved the PRP preparation technique, making it simpler and more reproducible than the described before [22]. The present study describes the clinical results of this new PRP preparation technique, using the PerMuTIS protocol.

Methods

Study design: This is a prospective case series study presenting the clinical results of the patients treated with PRP injections performed following the Multi Target clinical protocol and the Simple Double Spin PRP method described elsewhere [23]. This study composes the second part of the feasibility study of a randomized controlled trial project named ‘Biologic Therapy for Low Back Pain’, and follow the guidelines of the Biological Treatments Working Group of the American Academy of Orthopedics (www.mibo-statement.org) and the Standard Protocol Items Recommendations for Interventional Trials - SPIRIT Checklist [24,25]. This research was approved by the Institutional Review Board of Hospital Nossa Senhora da Conceição (Grupo Hospitalar Conceição, Porto Alegre) and registered at Plataforma Brasil (the Brazilian government’s registry of scientific studies) under CAAE (Certificado de Apresentação de Apreciação Ética - Certificate of Presentation of Ethic Appreciation) number 76715617.0.1001.5530.

Patients with more than 12 weeks of Low Back Pain, who failed conservative treatment were included. Inclusion and exclusion criteria are described in the Table 1-3.

Following the concept of the concurrent treatment of multiple degenerative and inflammatory pain generators in patients with LBP, PRP injections were done in facet joints, epidural space, paravertebral muscles and intradiscal, according to patients concerns, image scans and clinical data. Upon enrollment, all patients signed the written informed consent before collection of data. Baseline scores of pain and disability using the Visual Analog Scale (VAS) and Roland-Morris Disability Questionnaire (RMDQ) were recorded. The RMDQ is a widely used, reliable and sensitive self-reported questionnaire with a score that ranges from 0 (no disability) to 24 (extremely debilitated). Detailed evaluation of the lumbar spine MRI was conducted. Disc degeneration was rated according to the Pfirrmann rating for disc degeneration; disc pathology,

canal and foraminal compromise was described according to the nomenclature recommended by the combined task force of North American Spine Society (NASS), American Society of Spine Radiology (ASSR) and American Society of Neuroradiology (ASNR) facet arthropathy was graded according to the grading system for severity of facet joint osteoarthritis developed by Fujiwara, et al., and the degree of muscle atrophy according to Kader, et al., classification [26-28]. VAS and RMDQ scores were recorded at baseline and follow up evaluation at 6, 9 or 12 months. The structures selected for treatment were chosen according to patient presentation, physical examination, and imaging studies. The potential targets for the PRP injection included the facet joints, discs, spinal canal and paravertebral muscles. The criteria for target selection were as follows:

Facet joints axial LBP worse with trunk extension and prolonged standing, plus radiographic findings of facet arthropathy seen on Computed Tomography (CT) or MRI and/or Pfirrmann 3 or greater disc degeneration (due to the close association between facet arthropathy and disc degeneration). Ultrasound guided injection was used in almost patients. Longitudinal scan to mark the target level (Fig. 1) and Transversal scan to perform in plane injection (Fig. 2).

- Intervertebral disc - LBP worse with forward flexion and prolonged sitting, with or without radiculopathy, plus MRI findings of high-intensity zone or annular tear without extrusion and/or concordant pain on provocative discography.
- Epidural injection - Radicular pain, plus abnormal MRI findings, with or without signs of foraminal neural compression. The procedure route was transforaminal or via sacral hiatus; guided by ultrasound (Fig. 3,4) or fluoroscopy.
- Muscular injection - localized muscle pain worse with standing upright or physical activity plus tenderness to muscle palpation or presence of moderate to severe muscle atrophy (>10% replacement of muscle with fat or fibrous tissue) on MRI, according to Kader, et al.

PRP Preparation and Intervention: Blood was collected through peripheral venous access in tubes with ACD anticoagulant. The preparation process followed the Simple Double Spin protocol (Fig. 5). Control samples of basal blood and PRP obtained were separated to evaluate the concentration obtained.

The spinal injection was performed with the patient in a prone position and followed a strict sterile technique. Imaging guidance was used for precise localization of the targets using fluoroscopy and/or musculoskeletal ultrasound. The volume of PRP injected are as follows: 2 ml for foraminal injections (per site), 5 ml for caudal epidural injection, 2 ml for each facet joint and capsule, 2 ml for each site of paravertebral muscles and 1 ml for intradiscal injection (per disc).

Statistical Analysis: Quantitative variables were described as mean and standard deviation or median and interquartile range as appropriate. Categorical variables were expressed as absolute and relative frequencies. Student's t-test was used to compare means. The level of significance was set at 5% ($p \leq 0.05$) and all analyses were performed using SPSS, version 23.0.

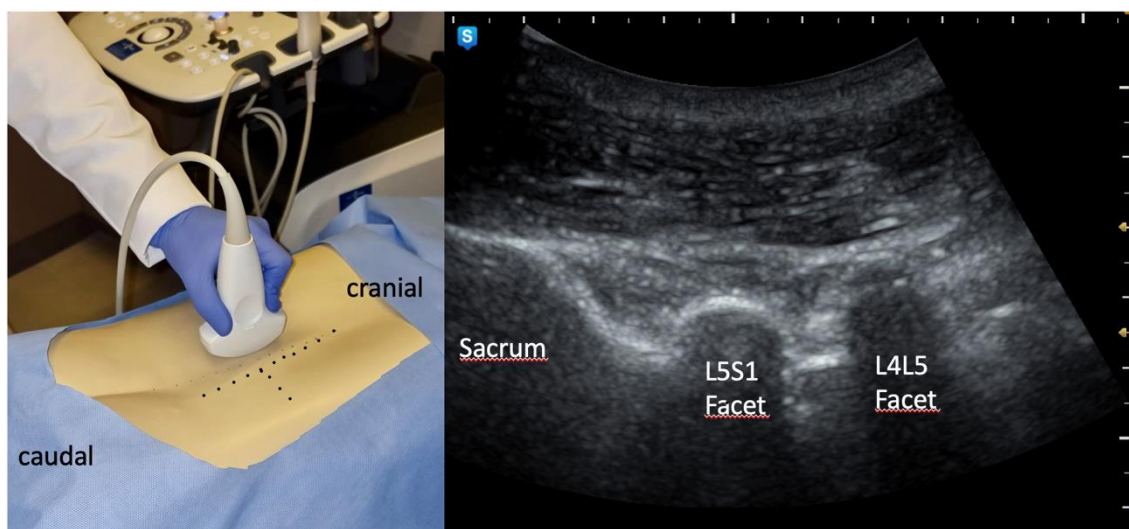


Figure 1: Sagittal / Longitudinal view - Identification of the injection level.

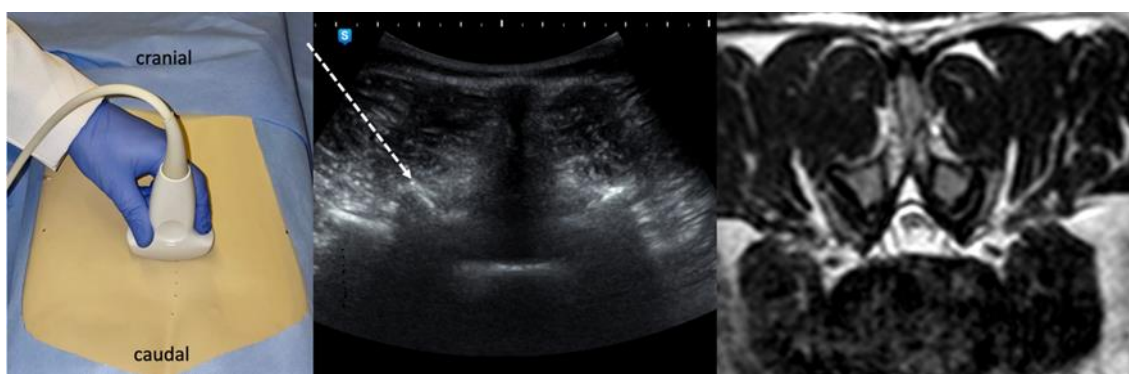


Figure 2: Longitudinal/Axial view - Identification of the needle path in plane - RMI image.

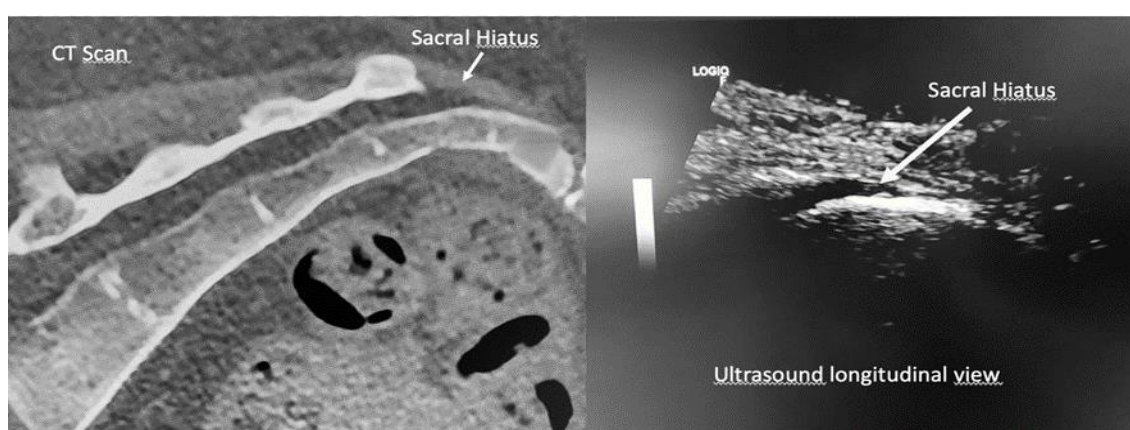


Figure 3: Sacral Space and Hiatus: CT scan and Ultrasound Scan.

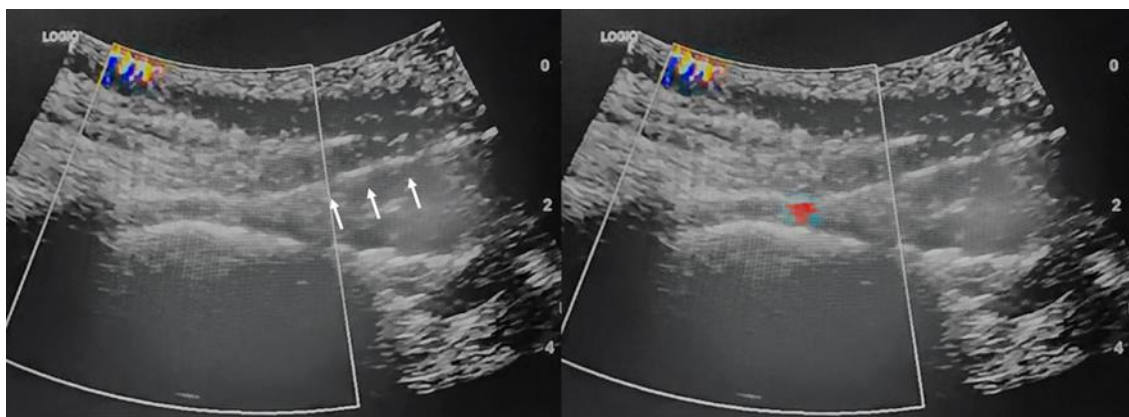


Figure 4: Longitudinal view; White arrows: Needle in the sacral hiatus; Right Picture: Doppler flow confirms correct positioning in the epidural space.

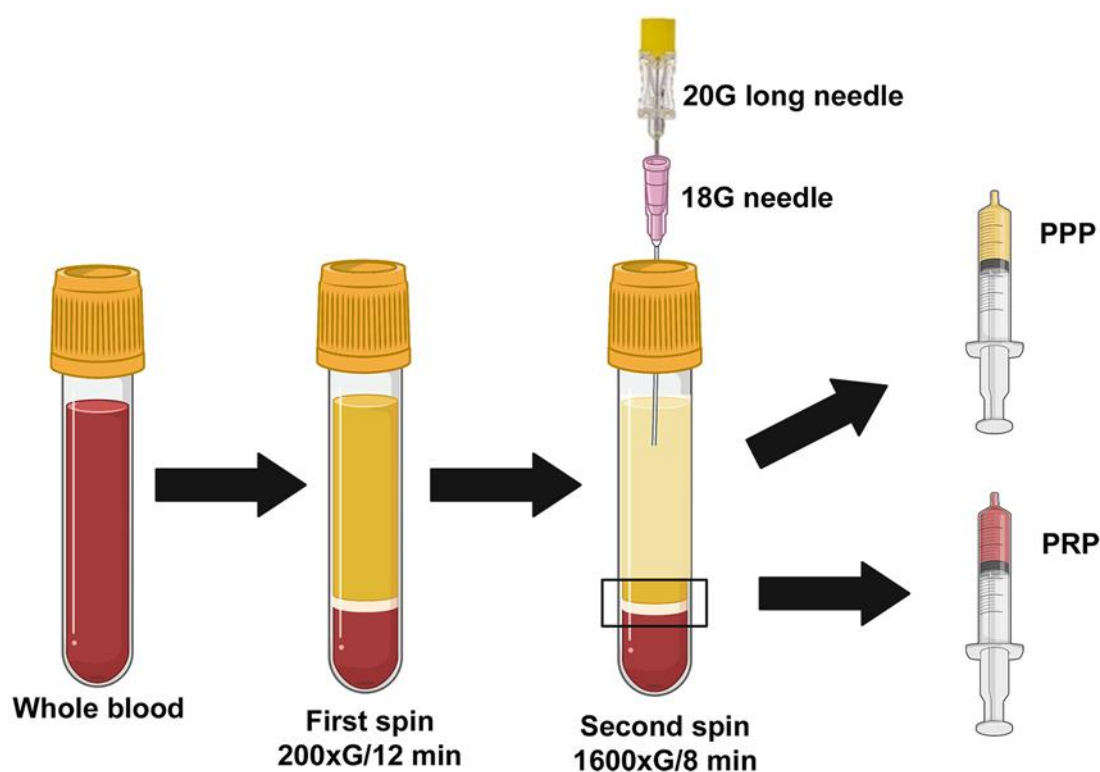


Figure 5: PRP preparation method: After whole blood is collected from volunteers, it undergoes the first spin at 200G for 12 minutes. Then, without any manipulation, it goes through the second spin at 1600G for eight minutes. Finally, with the assistance of an 18G needle (used as a guide), a 20G long needle is inserted to aspirate the PPP (Platelet Poor Plasma) and the PRP (Platelet Rich Plasma).

Inclusion Criteria	Exclusion Criteria
• Low back pain more than 12 weeks • Previous conservative treatments (oral medications, physical therapy, steroid injections) • Clinical evaluation indicates lumbar epidural, facet, intradiscal or paravertebral intramuscular injection	• Refusal to participate in research • Age: younger than 18 years old or older than 80 years old • Active infection • Neoplasm • Conditions requiring urgent surgery: cauda equina syndrome, spinal instability • Progressive neurological deficit • Severe stenosis • Allergy to contrast material or local anesthesia • Presence of unstable psychiatric condition • Hematologic disorders (thrombocytopenia, coagulation disorders, sickle cell disease)

Table 1: Inclusion and exclusion criteria.

Age (years) - mean $\pm$ SD	58,6 $\pm$ 17,4
Gender	n (%)
Male	7 (30,4)
Female	16 (69,6)
Follow-up (months) - median	12

Table 2: Patient demographics.

	Baseline	Post-Procedure	P-value
VAS score (mean $\pm$ SD)	8,3 $\pm$ 0,6	3,2 $\pm$ 1,1	<0,001
Roland-Morris score (mean $\pm$ SD)	19,1 $\pm$ 1,9	7,8 $\pm$ 2,7	<0,001

Table 3: Pain and disability baseline and post procedure.

Results

At baseline, all 23 patients (16 female) had moderate-to-severe pain (VAS range 6-9, average 8.3). The mean RMDQ score was 19 (range: 9-23) at baseline, indicating a severe disability according to the Roland-Morris grading scale. The majority of the patients had multiple abnormal findings on MRI. The most common abnormal MRI finding was facet arthropathy, followed by intervertebral disc degeneration (Fig. 6).

Mean VAS pain score across the cohort decreased by approximately 62%, while the Roland-Morris disability score decreased by about 60% at 52 weeks.

The average time of preparation of PRP was 30 minutes (since the venipuncture to the moment of injection). The final product obtained was Leucocyte-Monocyte Rich PRP. Platelet concentration in absolute values was 908,000/ μ L (814 -1020), or 4.2X baseline values. Monocyte concentration was 3.2X baseline values. No adverse events related to the application of PRP were observed in this sample.

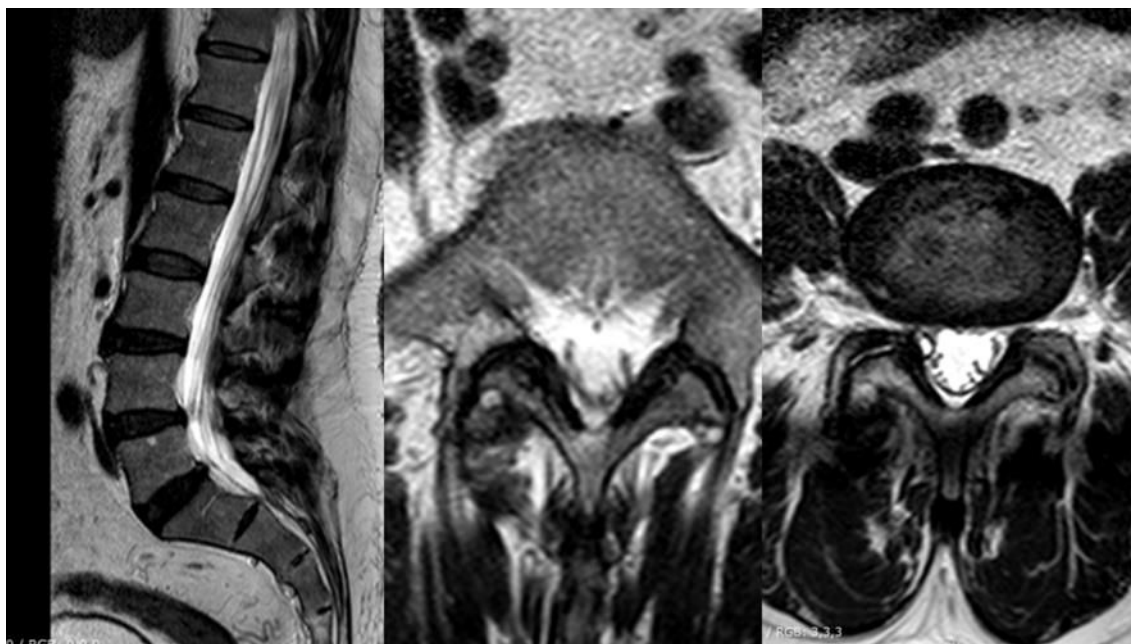


Figure 6: MRI showing in L4L5S1: Disc degeneration, muscle atrophy and facet arthropathy.

Discussion

The unique characteristics of degenerative spinal disease, which affects different anatomical sites, with different cellular and histological configurations, requires a personalized assessment of each patient. The current understanding of the degenerative process in the spine and the interrelationship between the different structures of the spine suggests that the vast majority of patients with chronic low back pain do not have only one pain-generating site. In our first case series, 81.8% of the patients presented alterations in two or more sites, with facet arthrosis (91.3%) and disc degeneration (60.9%) being the most frequent [21]. Evaluation of the cause of chronic LBP is complex due to many different structures involved and the multifactorial nature of the disease process. In this study, participants had more than one abnormality observed on MRI, which included facet joint arthropathy, intervertebral disc pathology, spinal canal stenosis and paravertebral muscle atrophy.

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When talking about degenerative spinal disease, many researchers focus only on the intervertebral disc. Numerous lines of basic, *in-vitro*, and *in-vivo* research are looking for alternatives to disc degeneration, but the translation to clinical practice seems far from reality. Perhaps the disc is the main player, but in the real patient, it is not the only one. So, proposals for single intradiscal injections may be reserved for selected patients, only with discogenic pain, with no other changes. In a double-blind, randomized clinical trial, 47 patients with discography-confirmed discogenic pain were selected to receive intra-discal or contrast PRP (control) [29]. The outcomes evaluated were improvement in pain by the NRS, improvement in disability (FRI and SF 36) and degree of satisfaction with the procedure using the NASS Satisfaction Questionnaire. The group of patients who received treatment (n=29) showed a significant improvement in these indices when compared to the control group (n=18) in the eighth week after the procedure. This study also offered patients in the control group the option of cross-over after the eighth week. More x patients were included in the therapy group. This group of patients was followed up and the results of the evaluations were published, with a follow-up of 5 to 9 years [30]. Numerical Rating Scale (NRS) pain scores, SF-36 pain, SF-36 physical function, and the Functional Rating Index were used to assess patients' pain and function at follow-up, and the Generalized Estimating Equations method was used to analyze all variables. Patients reported significant reductions in current, best, and worst NRS pain at 5-9 years after injection, as well as SF-36 pain scores. Patients reported significant improvements in function, as assessed using the SF-36 Physical Function Scale and the Functional Rating Index, at 5-9 years after injection. All improvements in pain and function met predefined criteria for clinical significance. Of the 19 patients who completed the 5 to 9 year follow-up survey, 58% expressed satisfaction with the intradiscal injection of PRP. Of the 21 patients with available follow-up data, 71% reported clinically and statistically significant improvement in pain and function at 5-9 years after injection and were classified as successes, while 29% underwent surgery at the affected levels during the follow-up period and were classified as failures. The PRP used had an average concentration of 5x (Harvest Technologies Corporation Plymouth, MA centrifuge). This historical series was recently compared with another series of patients from the same team who used an ultraconcentrated Leukocyte Rich PRP (LR PRP) with an average of 10x more platelets than the baseline level [31]. The improvement in pain in the historical series was 1.7 (p=0.063) and in disability was 33.7±12.3 (p=0.001). Although the baseline pain and disability of the new series were higher compared to the 2016 series, the percentage of improvement was more significant in both pain (p=0.004) and disability (p=0.016). Furthermore, the level of patient satisfaction was also higher in the new series (81% vs. 56%; $\chi^2=4.9$; p=0.027). This publication brings a discussion about the ideal concentration of platelets, for which there is still no consensus on these values and on their real usefulness. Jain et al. published another case series, with 20 patients undergoing intradiscal injection of PRP, where platelet concentration and clinical outcomes of pain and functionality were compared [32]. A positive relationship was found between higher concentration and better clinical outcome. The worst results were those with concentrations below <400 10^3 /IL. This study also alerts to the great variability in the concentrations obtained, even using standardized methods. In this case, the double centrifugation technique used a DrPRP kit (Dr PRP® USA

LLC). The author comments on the need to evaluate baseline platelet values and the concentration perspective to be obtained.

In addition to disc pain, the other most common cause of low back pain is facet pain. The relationship between structural disc failure and facet overload, with consequent degeneration, is well described [16]. Considering that the facet are synovial joints similar to the knee joint, and the beneficial effects of PRP have already been demonstrated in these joints, it is reasonable to imagine its usefulness in the control of low back pain of facet origin. A randomized clinical trial evaluated the efficacy and safety of autologous PRP compared to local anesthetic and intra-articular injected corticosteroids in lumbar facet syndrome in 46 patients [34]. These were selected after diagnostic facet blocks with 0.5% lidocaine. Subjects were randomized into Group A (PRP) and Group B (AL/Corticosteroid). There was outpatient follow-up for up to 6 months and the results were analyzed using VAS, RMQ, ODI and modified Macnab criteria. There was no statistical relevance at the pre-treatment moment. 21 patients completed follow-up in Group A and 20 in Group B. Compared with pretreatment, there was statistical improvement in VAS, RMDQ and ODI ($P < 0.01$). A significant difference were found between the 2 groups in the questionnaires mentioned above ($P < 0.05$). Group B had higher subjective satisfaction and objective success after 1 month (80% and 85%), but only 50% and 20% after 6 months. However, for group A, it increased over time (47.62% to 80.95%). There were no complications. The PRP used was from a 2-step centrifugation method, the collected blood was stored in anticoagulant tubes with sodium citrate and centrifuged first at 200G. Plasma was subjected to a second 400 G centrifugation to remove platelet-poor plasma. Group A used 0.5 ml of intra-articular PRP and group B 0.5 ml of a mixture of 0.5% lidocaine and betamethasone (5 mg/ml) at a concentration of (4:1). Another randomized clinical trial evaluated 144 patients with facet pain, comparing the use of PRP with hyaluronic acid [34]. Evaluation of results through VAS, ODI and Macnab with an average time of 18 months. Although the assessment scales have obtained similar results, there was a superior clinical improvement in the PRP group, with a higher rate of patient satisfaction ($p > 0.0001$).

As the paravertebral muscles are important dynamic stabilizers of the spine, their atrophy results in overload of the facets and discs, creating a vicious cycle in pain and degeneration. Hussein and Hussein studied the effect of muscle injections of PRP in the lower back [35]. They describe the results in 115 patients who underwent weekly injections of PRP, associated with physical therapy with walking. The overall success rate was 71% a year of follow-up. Patient satisfaction was 87.8%. Post-procedure control MRI scans showed an improvement in the previously existing multifidus muscle atrophy. More recently, Sun Jae Won, et al., published the results of a randomized clinical trial involving the use of PRP and prolotherapy in 30 patients with chronic nonspecific low back pain [36]. All pain and disability assessments were favorable to PRP at six months. This article reports the synergistic effect between PRP and prolotherapy in strengthening the fascia and ligaments of the lumbosacral region. One limitation is that the injections were done blindly. The effectiveness of these procedures can increase with access to ultrasound, where fascia and ligaments can be visualized, as well as the diffusion of medication in the desired region.

Another route of administration of PRP is the Epidural. It is known that patients with disc pathologies and root lesions have inflammatory cytokines in the epidural space. Epidural injection of anesthetics and corticosteroids is one of the most frequent procedures in the interventional management of low back pain. Due to the existence of an anatomical relationship between the intervertebral disc and the epidural space, an epidural injection can reach the disc. Based on these anatomical principles, Correa, et al., used PRP in patients with cervical and lumbar disc herniation, with epidural injection [37]. In his article, a good theoretical argument is made with all the logical basis supporting the indication of this path. A detailed anatomical review of the epidural space was even presented. In this case series 70 patients with cervical and lumbar hernia underwent epidural injection. The 6-month evaluations revealed complete relief of symptoms in 40% of patients. 15% still reported pain 2-3 on the Visual Analogue Scale, 25% pain 3-6 and 20% reported no change in pain. This was the first published study on the topic. This same group published two years after another case series, with 250 patients, approximately 175 of whom underwent lumbar PRP injection [38]. The injection had a volume of 12 ml of PRGF and was given a second dose 6-8 weeks later. Pain improvement at 12 months was from VAS 9 to VAS 2, MacNab criteria were from Poor to Excellent, and opioid use dropped from 96% to zero. In a review of a series of 470 patients who underwent epidural administration of platelet lysate, Centeno et al. showed that this is a good option for the corticosteroids currently used by most pain interventionists [39]. In his argument, he comments on the deleterious effects that corticosteroids can cause. Despite the popularity of the use of corticosteroids, there is no clear evidence of their benefits as a means of improving function, decreasing disability, or decreasing the rate of indication for surgical procedures. Some randomized trials have failed to show superiority to placebo and the use of corticosteroids is associated with a multitude of adverse effects ranging from altered functions of the endocrine, cardiac, musculoskeletal, gastrointestinal, dermatological and nervous systems. It is known about the effects on bone density and osteoporosis induced by the chronic use of corticosteroids. In this prospective study, 470 patients with radicular pain underwent epidural injection of platelet lysate and followed up for 24 months. Functional and Pain Assessments were performed (FRI Functional Rating Index, NPS Numeric Pain Score, SANE Single Assessment) and showed significant improvement in relation to the initial assessment ($p < .0001$).

Both in our study and in the literature, we see that the use of PRP in several sites that generate pain in the lumbar spine is obtained with clinical results, with few reports of complications. Its advantages over the use of corticosteroids or indication of major surgeries are well demonstrated.

Conclusion

The effects of Platelet Rich Plasma in the control of pain and the degenerative process of the spine have been demonstrated in several studies. The principle of application in multiple targets using a simple and low-cost preparation technique proved to be feasible and without reports of

serious side effects that compromise its indication. The PerMuTIS - Personalized Multi Target Biologic Injection in the Spine Technique using Simple Double Spin protocol demonstrated safety and feasibility in this prospective study of patients with low back pain who failed conservative treatments. Large scale, multicenter randomized clinical trial will provide an appropriate level of evidence to assist in clinical practice.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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