International Journal of Anesthesia and Clinical Medicine
2019; 7(1): 1-6
http://www.sciencepublishinggroup.com/j/ijacm
doi: 10.11648/j.ijacm.20190701.11
ISSN: 2376-7766 (Print); ISSN: 2376-7774(Online)

Epidural Plasma Rich in Growth Factors for Degenerative Disc Disease: A Valuable Alternative to Conventional "Palliative Medicine"

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To cite this article:
Correa Jose, Cortés Henry, Abella Patricia, García Edwin. Epidural Plasma Rich in Growth Factors for Degenerative Disc Disease: A Valuable Alternative to Conventional "Palliative Medicine". *International Journal of Anesthesia and Clinical Medicine*. Vol. 7, No. 1, 2019, pp. 1-6. doi: 10.11648/j.ijacm.20190701.11

Received: August 19, 2018; **Accepted**: October 23, 2018; **Published**: February 28, 2019

Abstract: It is only through the understanding of lumbar spine pathophysiology and its clinical correlates that specific rational treatment for patients becomes possible. Intervertebral disc disease (IDD) is a progressive, chronic, degenerative disease. Over time, the degeneration worsens and ultimately becomes irreversible. The pathogenesis of IDD involves a complex interplay of inflammatory, immunological, and pressure-related processes. Current treatments for IDD, proposed in most ´consensus protocols´ do not correspond to the pathophysiological process involved in the IDD, as these treatments are mainly focused on relieving pain (palliative pain medicine). Surgical techniques (including fusion, laminectomy, and discectomy), aim to stabilize the spine and/or decompress the spinal or the foraminal canal thus alleviating symptoms, but these techniques are not addressed to regarding the cause of the degeneration, and sometimes even accelerate the degeneration of the adjacent segments. Recently, biological therapies have been attracting more attention in the field of intervertebral disc repair and regeneration. Plasma rich in growth factors (PRGF) has the ability to repair and regenerate bone and condral tissue and has a remarkable neuroprotective and anti-inflammatory actions by modulating the immune response, reversing IDD and relieving the neuropathic pain. Growth factors have been associated with the initiation of a healing cascade that leads to cellular chemotaxis, angiogenesis, synthesis of collagen matrix, and cell proliferation. This paper briefly describes the current understanding of growth factors and our experience with PRGF injected by the epidural route.

Keywords: Plasma Rich in Growth Factors, Intervertebral Disc Degeneration, Axial Pain

1. Introduction

In the 1970s, Kirkaldy-Willis first described the "degenerative cascade" of the degenerative disc disease [1]. From an initial dysfunction of the disc (fissure of the annulus fibrosus losing the capacity of containing the nucleus pulposus (first stage), to comprising the mobile segment, disc and facet joint degeneration leads to dynamic spinal instability (second stage), the patient finally develops a multifactorial stenosis, which may or may not be associated to instability (third stage). The pathogenesis of IDD involves a complex interplay of inflammatory, immunological, and pressure-related processes [2].

Intervertebral discs are the largest avascular structure of the body; that means they have very poor regenerative capacity [3]. Disc cells depend on the blood supply at the margins of the discs for their nutrients. The nucleus and inner anulus of the disc are supplied by capillaries that arise in the vertebral bodies, penetrate the subchondral bone, and terminate at the bone-disc junction. *Despite being highly implicated in disc degeneration, the end plate has hardly been quoted into regenerative strategies [4-5].* Current therapeutic approaches should therefore be focused on combating the disc's poor nutritional supply, diffused from the blood vessels of the vertebral body through the

cartilaginous end plate. Plasma rich in growth factors (PRGF) is a recent cell-based technique being evaluated for promoting intervertebral disc healing, as PRGF has shown in vitro and in vivo the potential to stimulate intervertebral disc matrix metabolism [6-14). Upon activation, these platelets release a variety of cell signalling molecules such as platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), transforming grow factor (TGF-β1), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and basic fibroblastic growth factor (FGF) [15-19]. Also neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and other neurotropic factors such as fibrin, fibronectin, and vitronectin are active mediators [20-22]. These biological mediators of plasma govern tissue repair by mechanisms which are still poorly understood. However, evidence suggests that the biomolecules conveyed by PRGFs are instrumental agents that modulate early inflammation, stem cell-like myelinating SC activation, macrophage polarization, as well as the active resolution of inflammation, angiogenesis, and fibrogenesis. Likewise, the gelatinous hydrogel scaffold impregnated with PRGF has shown to facilitate the recovery of native biological and biomechanical functionality of the disc when it is injected intradiscally, as there is extensive loss of matrix and structural damages exhibited in advanced stages of disc degeneration (IDD).

This accumulated evidence in both preclinical and clinical settings indicates that PRGF and the fibrin scaffold have an important therapeutic role in patients with IDD, not only due to its potential to enhancing cartilage regeneration and to reducing the catabolic factors that lead to cartilage degradation, but also because of its neuroinflammatory therapeutic modulation and its neuroprotective, neurogenic, and an enhancer of sensory and motor functional recovery. Thus, the application of PRGF in patients with IDD, considered few years ago merely as an "off the shelf" alternative, should be, in our opinion, the current "flagship" in the multimodal therapeutic scheme for IDD. To date only a few cell-based clinical trials targeting IDD repair or regeneration have been published, most of which were through intradiscal PRP injection, and none with long term MRI follow-up. This research to improve our understanding of the biology of intervertebral disc healing and into methods to enhance the repair and the regenerative process of the intervertebral discs have conducted us to the use of biological therapies for the management of IDD.

This study is a clinical trial in which PRGF was injected into the epidural space for promoting IDD regeneration. We have a preliminary trial that included 70 patient treated with one epidural PRGF dose, and the trial focused on clinical perspectives (pain relief and assessment of patient satisfaction through VAS score and Macnab criteria) [13]. This current research reaches 250 patients who received two doses of epidural PRP and who were assessed with magnetic resonance imaging (MRI) one year after PRP treatment to find disc or facet join changes if they occurred. This is probably the most extensive follow-up document that links PRGF used in injection into the epidural space as a method of intervertebral disc regeneration in cases of disc disease, and the only one with MRI evaluation before PRGF treatment, and then one year posterior to the PRGF therapy. Even considering that it is a field of research still in early development, this study is a novel alternative treatment with promising clinical results for intervertebral disc disorders and far distant from the poor results usually achieved with current consensus protocols.

2. Study Design

Prospective observational, nonrandomized, single-center clinical study carried out between January 2015 and June 2017. We have included 250 patients, who were between 18 years to 70 years of age, with neck or back pain with or without radicular pain, and with a diagnosis of a spinal disc herniation confirmed with MRI imaging. After receiving institutional approval and informed consent signed by all patients, they were approached for enrollment. In the majority of patients the ethiopatogenesis of the axial or radicular pain was due to multifactorial origin: disc disease, facet joint arthrosis, hypertrophy of the ligamentum flavum, and in many cases associated to central canal narrowing or foraminal stenosis.

3. Method

Procedures were performed in the operating room with the patient in prone position. All patients received an epidural injection under LA using a 18G-Tuohy needle at cervical level (C6-C7) (30% of patients) or lumbar level (L4-L5 or L5-S1) (70% of patients). The epidural space was identified with the "loss of resistance" technique (Dogliotti) [23], and corroborated with fluoroscopic localization. The volume of autologous plasma injected was 10 ml in the cervical area and 12 ml injected in the lumbar area. A second epidural dose (booster dose) was performed 6 to 8 weeks after the first dose using a similar technique.

The patients were evaluated in terms of both pain and function using the VAS-scale [24] and a modify MACNAB-criteria (table 1). MRI follow-up have been documented in 50% of the patients one year after the second dose.

Table 1. *Modified Macnab Criteria.*

1. Excellent: No pain. No restriction of mobility. Return to normal work and level of activity.
2. Good: Relief of presenting symptoms. Occasional back or leg pain of sufficient severity to interfere with the patient's ability to do his normal work or his capacity to enjoy himself in his leisure hours. Able to return to modified work.
3. Fair: Improved functional capacity, but handicapped by intermittent pain of sufficient severity to curtail or modify work or leisure activities. Still handicapped and/or unemployed.
4. Poor: No improvement or insufficient improvement to enable increase in activities. Continued objective symptoms of root involvement. Probable further operative intervention needed, irrespective of length of postoperative follow-up.

4. Results

Epidural PRGF injections for IDD showed clinically significant improvements in pain (VAS-scale) and function (MACNAB-score) throughout two years of follow-up. Mean VAS-scale improved in 85% of patients, from 9 to 3, and the mean MACNAB-score was considered GOOD at six months and EXCELLENT at the end of one year after the epidural PRGF injections. The need for opioid rescue decreased from 96% to none at the end of one year follow-up (table 2). However, 15% of the patients did not improve the pain score; but no patient showed a worsening of the symptoms. Positive changes in MRI images one year following the second epidural dose have been documented in few patients, but this aspect needs further research.

Table 2. *Outcome of patients after Epidural PRGF injections.*

Outcome assessment	Mean VAS scale	Mean MACNAB score	Opioid rescue
Previous to PRGF injection	9/10	POOR	96% of patients
Two months after two doses of epidural-PRGF	4/10	FAIR	20% of patients
Six months after two doses of epidural-PRGF	3/10	GOOD	none
One year after two doses of epidural-PRGF	2/10	EXCELLENT	none

5. Discussion

Low back pain (LBP) is a prevalent, costly, and challenging condition to manage. Intervertebral disc disease (IDD) is a progressive, chronic disorder and number one cause of LBP. Current treatments for discogenic low back pain are predominantly conservative. However, to date, no medications have demonstrated efficacy in lumbosacral radiculopathy, which is probably the most common type of neuropathic pain (NP) [11, 25-26]. Epidural steroid injections (ESIs) are the single most common injection for back and neck pain in the United States and elsewhere [27]. The injection is performed to reduce swelling around a spinal nerve due to a bulging or herniated disc or pressure on a nerve due to bone spurs, considering that steroids are potent anti-inflammatories. Undoubtedly this is the most popular technique for the last 50 years in the USA, where over 2 million claims submitted to Medicare for ESIs in 2012 alone [28]. This widespread use of epidural injections of steroids (in combination with opioids and/or local anaesthetics) is not, however, free from side effects. Pain relief is usually only temporary and lasting no more than 6 months. Also, ESI can be associated with serious side effects, some catastrophic, even fatal, neurological complications including stroke and paralysis. These injuries are thought to occur by a variety of mechanisms, out of the context of this document. It is our opinion that for many, perhaps even for the majority of patients scheduled for ESIs, the pathophysiology of their pain is not studied/ understood and thus there is difficulty predicting for a given patient whether the ESI technique will confer benefit. Spinal surgery seeks only to alleviate painful symptoms without restoring disc mechanics or structure. Thus, recurrent episodes of pain are common and adjacent levels of the spine can experience accelerated degeneration [11]. Therefore there is a strong need for therapies that both alleviate painful symptoms and restore disc structure and mechanical function by directly addressing the underlying biological causes of disc degeneration. Among current biologic therapies, there is an emerging minimally invasive strategy that consists of infiltrating plasma rich in growth factors. This clinical evidence for PRGF treatment of discogenic low back pain in humans has been reported since 2011 [29]. There are many in vitro and in vivo studies have confirmed the efficacy of PRGF in IDD management. The injection of PRGF is really a good option in patients qualified for PRGF preparations as unlike other bioactive factors with complicated or unstable properties used for the clinical treatment of damaged tissues, as PRGF can be quickly obtained in the operating room by centrifugation of the patient's own blood and directly applied to target tissues.

In IDD patients, the neuraxial administration of PRGF is a convenient and relatively less invasive therapeutic procedure compared to other invasive options. Intradiscal injection of autologous PRGF in patients with low back pain is safe and free of adverse events. [9-11, 29-31]. Epidural injection of PRGF is another option that have been investigated, although research works in this respect are scarce. This, our current line of work, is a clinical trial investigating for improvement of pain and functional recovery of the patient. Our hypothesis is that, compared to intradiscal injection, growth factors by epidural route would fulfill an effective outcome by acting not only on the discs, but also over the facet joints and the ligamentum flavum, and, because of its anti-inflammatory activity, this technique would help with relieving NP [32]. This is due because the effects of PRGF activity on target organs occur despite indirect delivery, as the growth factors have not an autocrin activity, but a paracrine activity. Thus, we consider that "multi-factorial conditions need multi-factorial treatments", and the choice of the epidural space is therefore based on a good knowledge of the anatomy of the spine and its content, as well as the pharmacodynamics of the medication we are using. Nevertheless, no clinical study have so far indicated the number of injections required.

Intradiscal PRGF vs. Epidural PRGF

Neuraxial drug administration was initially developed in the form of spinal anaesthesia 100 years ago. Since then, evolvement of neuraxial drug administration now includes a wide range of techniques to administer a large number of different drugs (local anesthetics, opioids, a2-agonists, baclofen, ketamine, midazolam, neostigmine, adenosine, steroids, ziconotide) not only to provide anesthesia, but also

to provide analgesia and to treating a variety of acute and chronic settings. A solid understanding of the pharmacology of neuraxially administered drugs should be ideal in the practice of anesthesiology as it informs the clinician in choosing the proper agents to safely achieve analgesia and anesthesia in a wide variety of settings. Although epidural techniques are common in our daily practice and in spite that pharmacokinetics of epidurally administered drugs has become the subject of many studies, little is known about this topic as the levels and concentrations of drugs administered in the epidural space has never been measured. Pharmacodynamics, on the other way, places particular emphasis on dose–response relationships, that is, the relationships between drug concentration and effect on the organism, and the pharmacodynamics of drugs administered by the epidural route has mainly been based according to the effects of the chemical substance administered by this route on the target organs. Taking into account all these considerations and provided that our understanding of epidural pharmacokinetics is far from being properly understood, we should add here the recent biological therapies, including cell-based therapy, that have been added to the list of neuraxial techniques, in an effort to prevent or even reverse the progressive trend of intervertebral disc disease (IDD). In the case of PRGF's, most current researches using regenerative techniques for IDD have been focused on injecting it intradiscally. However, due to the short half‑life of the growth factors released from plasma, multiple injections of these biologically active substances should probably be necessary to effectively regulate the metabolic balance of the extracellular matrix and maintain the homeostasis and functional outcome of the discs. In this respect, in the long term follow-up, the intradiscal injection is not likely the best option as some studies have reported that needle puncture of the disc could induce cell death and degeneration. In this regard, the epidural technique would be a more suitable method. Yet, no clinical study has so far indicated the number of injections required, and so future randomized controlled clinical studies should be performed to systematically evaluate the effects of this therapy. Injecting PRGF into the epidural space has other advantages, especially for multi-segment disc degeneration, since it can be used repeatedly and probably with less adverse side effects than multiple punctures of the disc. The absorption after the injection of plasma into the epidural space is fairly guaranteed. Here, probably, the discussion on the absorption and distribution of the epidural plasma is more an issue of "where does the dose go". After injection, the drug solution coats the cylindrical dural sack, spreading up and down (as well as anteriorly to encircle the cord) in a fairly random fashion (Quinn Hogan 2002). Therefore epidural plasma would permit an effective activity not only on the discs, but also over the facet joints and the ligamentum flavum, and, because its anti-neuroinflammatory activity, would help us with relieving NP.

The four main lines of evidence that support this therapeutic potential of plasma rich in grouth factors (PRGF) administered in the neuraxis are [14], [21]:

1. PRGF control inflammation (through cytokines release).
2. PRGF modulates the immune system (inflammation has a neurotrophic and neuroprotective effects but this inflammatory activity can also result in neuronal damage that could develop to the persistence of NP).
3. PRGF stimulates regeneration.
4. PRGF reduces scarring.

Evidence based approach to growth factors in neuroaxis

1. Many growth factors (GFs) such as platelet derivated growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF), vascular endothelial growth factor (VEGF), participate in the in the angiogenesis of the new capillaries, in the synthesis of collage, the chemotaxis and the formation of the bone matrix. Angiogenesis has shown to influence the resorption of herniated intervertebral discs [33]. Here, the most compelling and studied hypothesis, states that the extruded disc material into the epidural vascular space of spine is recognized as a "foreign body" and induces an inflammatory reaction by the autoimmune system. The inflammatory reaction and the neovascularization produces retraction of a herniated disc into the intervertebral space. Nevertheless, the precise mechanisms of disc regression are unclear.
2. The vascular endothelial growth factor (VEGF), a major regulator of new blood vessel growth and an important inducer of vascular permeability, has been recognized in the last few years to have additional non-vascular functions. VEGF can act directly on neurons by mediating its neuroprotective effect, and alternatively, by inducing angiogenesis and thereby allowing increased oxygen and nutrient transportation to the hypoxic tissues [34].
3. Insulin-like growth factor-1 (IGF) stimulated proteoglycan synthesis in cultured cells of the nucleus pulposus of bovine intervertebral discs in a dose-dependent manner, and the effect was inhibited by an anti-insulin-like growth factor-1 monoclonal antibody [35].
4. Intrathecal administration of transforming growth factor β1 (TGF-β1), a potent anti-inflammatory cytokine, have demonstrated to alleviate nerve injury-induced neuropathic pain in rats, attenuating nerve injury-induced neuropathic pain [36]. TGF-β1 acted as a powerful neuromodulator and rapidly (within minutes) suppressed chronic constriction injury - evoked spinal synaptic plasticity and dorsal root ganglion neuronal hyperexcitability, alleviating early- and late- phase neuropathic pain symptoms, such as allodynia and hyperalgesia, for several weeks in murine models.
5. Several growth factors present in plasma including the nerve gowth factor (NGF), brain derivated neurotrophic factor (BDNF), PDGF, VEGF, IGF-1, transforming growth factor beta (TGFB) alone or in

combination have been shown to exert an antiapoptotic and neuroprotective effect on mesenchymal stem cells (MSCs), neurons, the schwann cells (SCs), and human neural stem cells [21, 37].

6. With these considerations in mind, physicians along with patients should carefully examine the different alternatives and the different risks and benefits of the procedures to decide which the most favorable is given the patient's clinical status.

This evidence based medicine (EBM) document is according to the conception of reasonable use of modern, best evidences in making decisions about treatment of individual patients [38-47], trying to give our patients the best possible solution to this pressing clinical problem.

6. Conclusions

Epidural PRP injections for IDD showed clinically significant improvements in pain (VAS-scale) and function (MACNAB-score) through two years of follow-up. The second-dose injection improved functional outcome, however, to the best of our knowledge, no clinical studies have so far indicated the number of injections required. MRI changes require further research as long-term studies are lacking and should be a priority for future research. No complications were recorded during this study.

Conflicts of Interest

The authors declare that they have no competing interests.

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