Chapter

Perspectives of Cell-Based Therapy for Degenerative Diseases of the Spine: The Reason for Choosing the Epidural Space

José Correa, Henry Cortés, Lucia Correa and Rita López

Abstract

Intervertebral disc degeneration (IDD) is a chronic disease that causes significant disability and dependence and exerts a high cost on society. Concerning IDD, it is the most common cause of back pain, involving any segment of the spine. It is one of the most frequent reasons for consultation in the general population, second only to headache, affecting 80–85 % of people throughout life. Current therapeutic strategies focused on IDD are primarily conservative, including physical therapy and antiinflammatory medication. Surgical techniques intend to stabilize the spine and/or decompress the spinal or foraminal canal, searching for relieve of symptoms; however, do not address the cause of the degeneration and even accelerate the degeneration of adjacent segments. Understanding of the biology of platelet-rich plasma (PRP) and other growth factors conducted usto use of PRP as a promising biological therapeutic strategy for enhance the regenerative process, searching the healing of the intervertebral disc. With current few in vitro studies, and fewer clinical studies linking the bases of regenerative medicine (RM) in the management of degenerative disc disease, our pioneering research was to state the bases, fundamentals, results, and the new trends around the RM techniques focused on the pathology of the spinal canal, taking the advantages that offer the epidural route.

Keywords: epidural space, intervertebral disc degeneration, intervertebral disc regeneration, platelet-rich plasma, tissue engineering

1. Introduction

Low back pain (LBP) has become a major public health issue for people under 45 years. This global problem has an estimated prevalence of about 7.5% in the global population (WHO, 2017). LBP is a costly and challenging condition to manage. LBP has become one of the main reasons for limiting of physical activities and is spreading in epidemic proportions [1, 2]. With these concerns in mind, it is important to

highlight that lumbar disc degeneration is the most common cause of low back pain. Intervertebral disc disease (IDD) is a progressive, chronic disorder and number one cause of LBP.

Understanding of the IDD pathophysiology and its clinical course will allow us to focus on a rational treatment for the patient, when possible. Current treatments for IDD proposed in most consensus protocols do not correspond, unfortunately, to the pathophysiological process involved in the IDD, as these treatments are mainly focused on relieving pain (palliative pain medicine) [3]. Recent studies addressing the treatment of LBP, as opposed to current protocols, focus their management strategy based on the genesis that triggers pain. These pioneering studies [4–6] show that epidural PRP injections can improve significantly in the pain score (VAS-scale) and function (MACNAB-score) in patients with IDD diagnosis.

The aim of this chapter is to overview our pioneering research, the bases, fundamentals, and results. Also, this research includes the near future around the regenerative medicine (RM) techniques associated to the medullary canal. This research document also aims to highlight the new trends what the Regenerative Medicine focuses on the pathology of the spinal canal.

2. Historical overview

2.1 The evolution from general anesthesia to spinal techniques

... at past, surgeries were horrible ...

The beginning of Anesthesia dates to ancient civilization, seeking to alter the consciousness to prevent pain during surgery. Deliriant herbs as the sleeping sponge (Hippocrates), opium, belladonna, scopolamine, cannabis were the herbal remedies as anesthetics (**Figure 1**). At the XVI century appeared ether (Paracelsus) through the distillation of alcohol and sulfuric acid. Already in 1796 Davy discovered nitrous oxide (N2O) opening the doors to the future of anesthesia [7].

The knowledge of the chemical agents that altered the consciousness, and later the control of mechanical ventilation, through pulmonary insufflation, allowed the use of other drugs, no longer focused to pain control, but to facilitate the conditions of surgery. Appeared then the use of muscle relaxants and other drugs that allowed the control of the hemodynamic conditions of the patient. It came up the concept safety during surgery, the beginning of monitoring.

Figure 1.
Preventing pain during surgery: From the use of opium poppy and other herbal remedies (early civilization) to the first public demonstration on October 16, 1846, at Massachusetts General Hospital (modern anesthesia). The history of anesthesia.

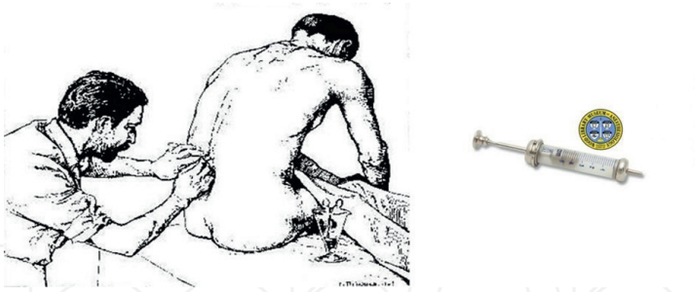

Figure 2.
Epidural technique: Towards the improvement of needles and the refinement of local anesthetic.

It was only from the end of the XIX century, with the development of needles and syringes, that allowed the introduction and safe use of regional anesthesia techniques epidural and spinal- with doctors F. Pagés and M. Dogliotti [8]. In the year 1899 and then at the year 1901 appeared the first publications on the use of spinal anesthesia and epidural anesthesia, respectively. Spinal techniques marked then a global milestone concept in the practice of anesthesia, at surgical activities but also in the developing of the Pain Units.

2.2 Overview about spinal anesthesia

Associated to the improving of the spinal technique (methods of performing, access route, dose, and the quality of the anesthetic substances) over time, the spinal pathway gained a prominent place, not only in the surgical field, but in other medical areas such as traumatology, rheumatology, pediatrics, internal medicine and oncology (**Figure 2**). Also, with the improvements of the spinal techniques, they reached the *gold standard* procedure in the Pain Units, as they allowed a continuous analgesia when necessary.

With the development of spinal techniques, injecting drugs into the epidural space is one of the most used interventions by anesthesiologists: local anesthetics, opioids, steroids, 'muscle relaxant'(baclofen), benzodiazepines (midazolam), clonidine, adenosine, ketamine, ziconotide, etc. Also, a specific mention to "hematic patch" in the management of post-dural puncture headache. In this way, the epidural space can be used, not only to provide anesthesia, but also to provide analgesia and to treating a variety of acute and chronic settings. In this context, the anesthesiologist should have a solid knowledge of the administered drugs within the epidural space.

Here we must add, then, another 'new drugs' to use into the epidural space: the biological therapies, the cell-based therapy.

3. Pathology of the medullary canal

Diseases engaged to the medullary canal, involved therefore to the epidural space, can be summarized as follows [9]:

1. Infection

2. Non-infectious medullary inflammation

3. Vertebromedullary trauma

4. Discovertebral degenerative processes

5. Inflammation of tumoral origin.

6. Postoperative spine

7. Congenital or acquired vascular pathology

It is not the aim of this chapter to deepen the study of the pathology of the medullary canal, but it is important to illustrate the changes that are linked to the degenerative processes of the discovertebral segment (number 4) in order to focus and understand what the vanguardist Regenerative Medicine therapy offers in the processes of the discovertebral impairment. In this regard, our goal is then to highlight the benefits of using the epidural space when we inject growth factors into the spinal segment. (Correa et al).

4. Degenerative disease of the spine

The spine is an articulated and highly resistant system, extending from the head to the pelvis. It plays a major role in protecting your body and supporting its movements. In between each vertebra of your spine lies an intervertebral disc. These discs allow the spine to generate movement and have flexibility. In addition, these discs serve as shock absorbers, protecting your vertebrae during everyday activities.

Spinal discs consist of a strong fibrous cartilage (the annulus fibrosus) which encloses a gel-like inner layer (the nucleus pulposus). As we age, these discs can weaken and become injured because of our personal habits, activities, diseases, and genetics. Degenerative disc disease is a painful degenerated disc. Degenerative disc disease is then an umbrella term that point out the pain that could extend from the neck to the lower back, associated with disc damage (**Figure 3**).

In the 1970s, Kirkaldy-Willis first described the "degenerative cascade" of the degenerative disc disease (DDD) (**Figure 4**) [10]. From an initial dysfunction of the disc, the 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) (**Figure 3**).

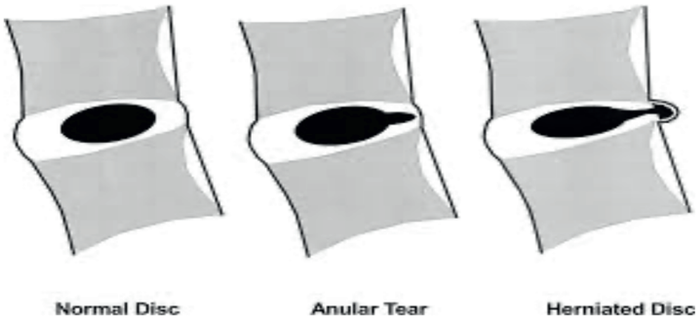

Figure 3.
DDD: The evolution of the disc damage.

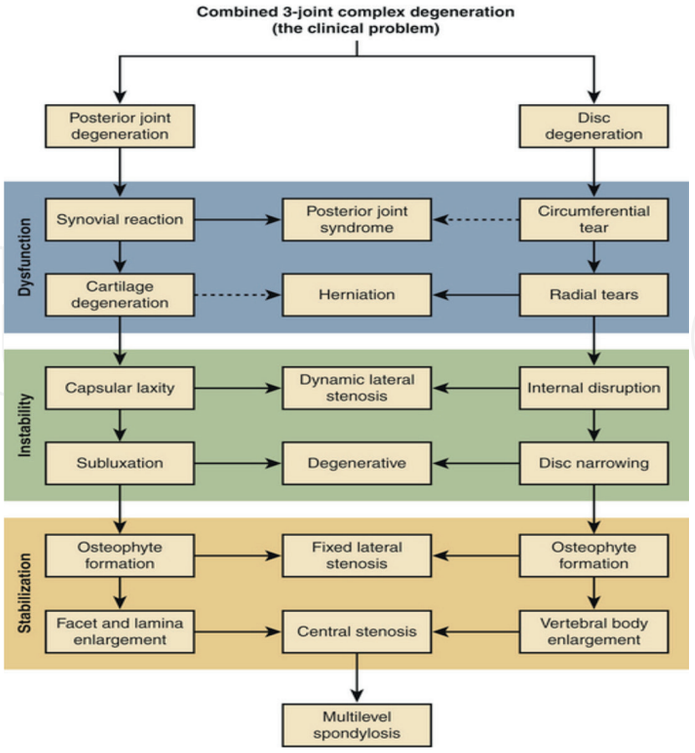

Figure 4.
Kirkaldy-Willis spine: The "degenerative cascade".

In this regard, the pathogenesis of the intervertebral disc disease process (IDD) involves a complex interplay of inflammatory, immunological, and pressure-related processes [11].

In anatomical terms, intervertebral discs are the largest avascular structure of the body.

Intervertebral disc, the flat, rubbery piece, that separate the bones of the backbones, have a very poor regenerative capacity [12]. 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 [13, 14].

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. However, the 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.

So, it is only through the understanding of the spine pathophysiology and its clinical course that will allow us to provide a rational treatment for patients.

At present, treatment options for degenerative disc disease remain suboptimal, and development and outcomes of novel treatment options currently must be considered unpredictable.

5. Understanding platelet-rich plasma (PRP)

The biology of platelet-rich plasma and its effect in the process of healing is a promising biological therapeutic strategy for enhance the regenerative process and healing of the damaged tissue (**Figure 5**).

The regenerative potential of PRP is based on the release of growth factors that occurs with platelet rupture. The first clinical report of PRP used as tissue regenerative therapy was published in 1998 by an oral surgeon who incorporates PRP into spongy bone grafting to reconstruct large mandibular defects [15]. Since then, PRP has been widely used in oral and maxillofacial surgery to improve osseointegration of dental implants and accelerate the healing process [16, 17]. More recently it has been used to treat injuries to the musculoskeletal system. Thus, at present, the use of PRP as a tissue regeneration therapy is well accepted for its modulating and stimulating properties of cell proliferation of mesenchymal origin (fibroblasts, osteoblasts, endothelial cells, epithelial cells, adipoblasts, myocytes and chondrocytes, mainly).

Platelet Rich Plasma (PRP) is then, the novel therapeutic tool of autologous nature that is strongly emerging in recent years with a successful therapeutic use. Different PRP studies have showed a beneficial effect on the target cells, which allows to propose its use the treatment of several pathological processes: the healing of wounds, the processes of tissue regeneration, or in the treatment of cellular involution that takes place with aging [18]. Clinically, PRP has been shown to decrease pain and increase function in chronic elbow tendinosis patients. PRP has also been used in plantar fasciitis, spinal fusion, and in total knee arthroplasty with varying degrees of success. PRP accelerated wound healing of human skin punch wounds in a recent prospective, controlled study.

In conclusion, the rationale behind the use of PRP is the deliver a high concentrations of growth factors and cytokines which can improve the healing process.

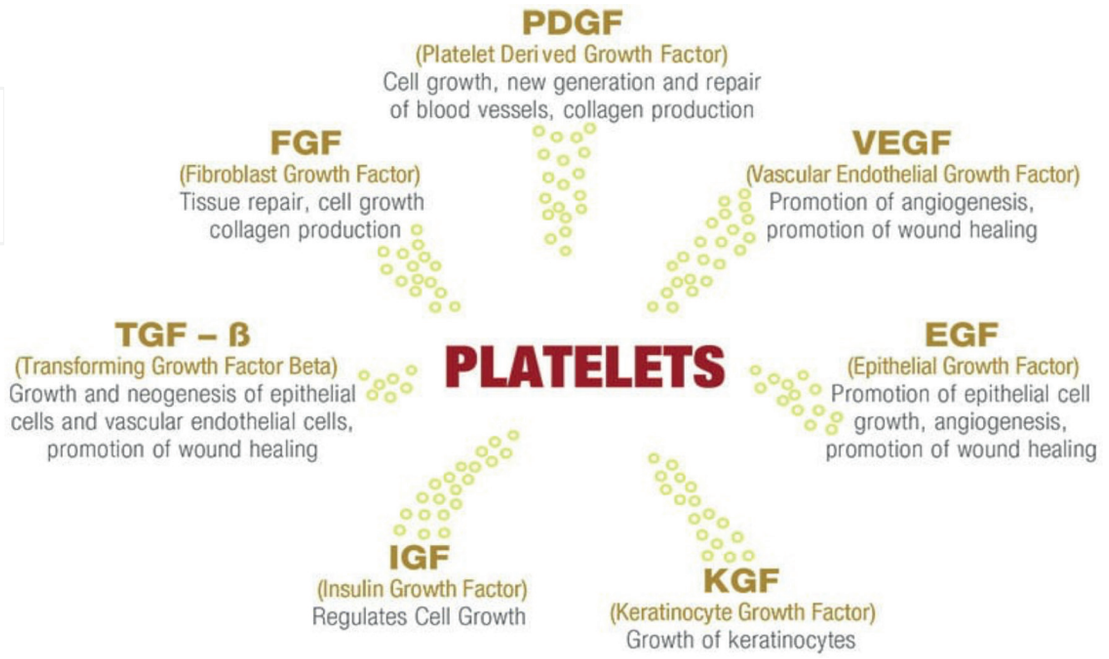

Figure 5.
Platelet-rich plasma: Growth factors and pro- and anti-inflammatory properties.

5.1 Tissue and cicatrization engineering around PRP

5.1.1 Regeneration: the healing process

Plasma rich in growth factors (PRGF) is a recent cell-based technique being evaluated for promoting tissue healing, as PRGF has shown in vitro and in vivo the potential to stimulate matrix metabolism [19–24]. Upon activation, these platelets release a variety of cell signaling 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). Other mediators, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and other neurotropic factors such as fibrin, fibronectin, and vitronectin, are also activated [24–26]. All these plasma biological mediators govern tissue repair although their mechanisms of action in the healing process are still poorly understood.

5.1.2 The anti-inflammatory effect with PRGF

Evidence suggests that biomolecules conveyed by PRGFs are instrumental agents that modulate early inflammation [27], also involved in the macrophage polarization, angiogenesis, and fibrogenesis, the stem cell-like myelinating SC activation, and finally, they have an active rol in the resolution of inflammation. Considering this benefit (anti-inflammatory effect) on the spinal axis intrathecal administration of transforming growth factor β1 (TGF-β1), a potent anti-inflammatory cytokine, has demonstrated to alleviate nerve injury- induced neuropathic pain in rats, attenuating nerve injury-induced neuropathic pain [28]. 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. These previous studies -in murine models-, allowed us to raise the hypothesis that PRP could help us to relieve neuropathic pain that is associated with DDD [29].

5.1.3 The neuroprotective effect of PRGF

Several growth factors present in plasma including the nerve growth factor (NGF), brain derivate 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 [25, 30].

6. Epidural PRP

The clinical evidence for PRGF treatment of discogenic low back pain in humans was reported in 2011 [31]. Since then, many research papers, in vitro and in vivo studies, have confirmed the efficacy of PRGF in IDD management. However, early in vivo studies used intradiscal injection of PRGF. These early documents concluded that intradiscal injection of autologous PRGF in patients with low back pain is safe and free of adverse events [29–33]. However, the intradiscal injection of PRGF technique is a more laborious proceeding and probably limits the effects. The first document injecting PRP into the

epidural space was our paper [4]. Knowing the biology of platelet-rich plasma and its restorative effect on cartilages (in general) and its repairing effect on the vertebral disc (in particular) allowed us to propose the use of PRP into the epidural space.

6.1 Why PDGF into the epidural space?

The choice of the epidural space needs a good knowledge of its anatomy and its content, as well as the pharmacodynamics of the medication we are using.

The first published study using the epidural space while injecting PRGF was our paper [4]. Our first line of work was only a clinical trial, assessing the pain relief response and assessing the degree of functional recovery of the patient. Our reason for changing the intradiscal injection technique, preferring the epidural space was 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. That further study had allowed us to confirm that this technique -epidural PRP- help with relieving the neuropathic pain (NP) associated to IDD [29].

6.2 Axial structure: the "poly-articular component"

We have considered the axial region as a "multi-articular component", where the epidural space would be an ideal place to inject PRP (**Figure 6**). The epidural space will allow us to reach the intervertebral disc, but also the facet joint, and even more, we can get the benefit of PRP in the foraminal region. Thus, the epidural space permits a pharmacological manipulation of various segments of this region, considering its inter-cellular signaling pathway.

6.3 Plasma rich in growth factors: the chemical signaling

Inter-cellular signaling is the communication between cells. The main difference between the different categories of signaling is the distance that the signal travels

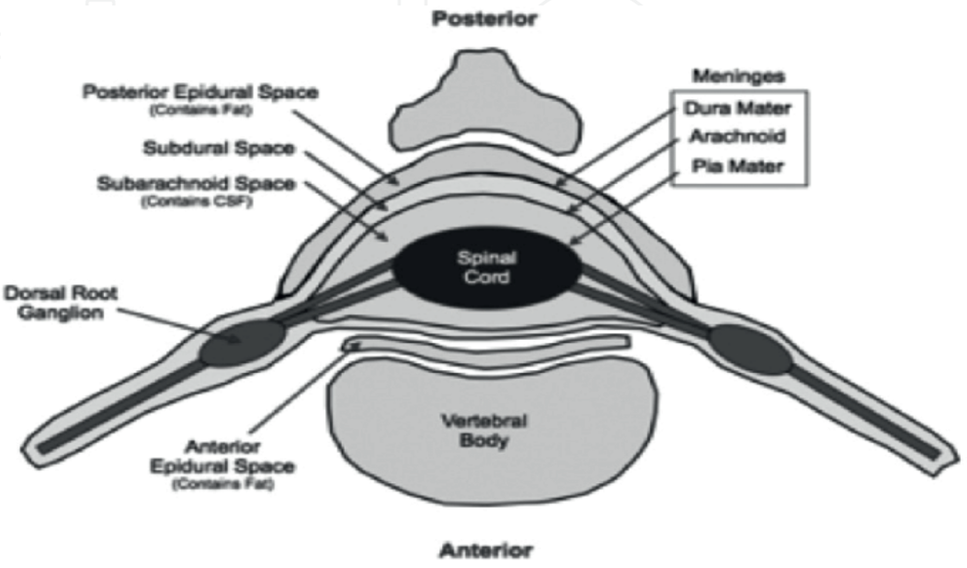

Figure 6.
Anatomy of the axial region.

through the organism to reach the target cell. In chemical signaling, a cell may target itself (autocrine signaling), a cell connected by gap junctions, a nearby cell (paracrine signaling), or a distant cell (endocrine signaling).

Multiple studies have demonstrated a beneficial effect of many of these growth factors, e.g., platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs), and granulocyte-macrophage colony stimulating factor (GM-CSF) on the healing process, accelerating wound closure with increased reepithelialization, cell infiltration, granulation formation, and angiogenesis. In all stages of the repair, a wide variety of different growth factors and cytokines are involved. The release of these various growth factors, cytokines, and low-molecular-weight compounds from degranulating platelets, are the mediators for the healing process. Fibroblasts, osteoblasts, endothelial cells, leukocytes, monocytes, and macrophages are cells involved in the produce of growth factors.

Growth factors and cytokines work as paracrine signals, that means they act locally, between cells that are close together [34]**.**

With these two concepts in mind (the axial structure and the way to act of the PRP) we considered that growth factors by epidural route would fulfill our expecting outcome.

Using PRGF in patients with IDD was considered, few years ago, merely as another "off the shelf" alternative. Recent studies, and our clinical results, now we have a different opinion: PRGFs should be the "flagship" within in the multimodal therapeutic scheme for IDD. Accumulated evidence, in both preclinical and clinical settings, indicates that PRGF and fibrin scaffold have an important therapeutic role in patients with IDD: (1) its potential to enhancing cartilage regeneration, (2) reducing the catabolic factors that lead to cartilage degradation, (3) its neuroinflammatory therapeutic modulation, (4) its neuroprotective effect. With these effects in mind, we achieve the sensory and motor functional recovery. However, only a few cell-based clinical trials targeting IDD repair or regeneration have been published, and most of them use axial PRP through intradiscal injection. Also, none of them have the long-term necessary MRI study in the clinical follow-up. In our understanding, we decide to use the biological therapy by the epidural approaching in the management of IDD. Injecting PRP into the epidural space means cytokines (inflammation control) and high concentrations of growth factors (tissue repair and regeneration). Epidural PRP allows us to suggest this is the first-line technique in the healing process of IDD.

PRP is a rich source of growth factors that promote tissue regeneration. Also, PRP suppress cytokine release, limiting inflammation, improving thereby, the healing process. So, Epidural PRP allows us to suggest this is the first-line technique in managing IDD.

6.4 Our designed study with PRP within the epidural space

The preliminary study, a clinical trial in which PRGF was injected into the epidural space for promoting IDD regeneration, started since 2014, and published in 2016 [4]. That preliminary trial included 70 patients, and they were injected with one epidural PRGF dose. That pilot trial focused on clinical perspectives (pain relief and assessment of patient satisfaction through VAS score and Macnab criteria).

Then, a new and larger study [5] reached 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. That was 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 was a field of research, still in early development, our novel alternative treatment with promising clinical results for intervertebral disc disorders was far distant from the poor results usually achieved with previous consensus protocols, those based on palliative pain medications, but not focused on treating the underlying disease.

6.5 Design of the second study

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 etiopathogenesis 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.

6.6 Results of the preliminary study

Epidural PRGF injections for IDD showed clinically significant improvements in pain (VAS-scale) and function (MACNAB-score) (**Table 1**) 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.

With these results, our pilot study showed a definitive role of PRP injection via the epidural space for chronic prolapsed intervertebral disc patients.

1. Excellent: No pain. No restriction of mobility. Return to normal work and level of activity.
2. Good: Relief of current 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 increasing activities. Continued objective symptoms of root involvement. Probable further operative intervention needed, irrespective of length of postoperative follow-up.

Table 1.
Modified Macnab criteria.

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

Table 2.
Outcome of patients after epidural PRGF injections.

7. Conclusions

1. Consensuses, in general, need to be updated periodically [35].

2. Pain Units are having great changes. Palliative management of pain has specific indications, but far from the goal of managing osteoarticular degenerative diseases. Mere palliative management of pain in osteoarticular degenerative disease is then, the second line option. Introducing the development of Regenerative Medicine (RM), regenerative therapies (mesenchymal stem cells and many growth factors from stem cells) which allow to promote and improve the healing process, may become a new current therapeutic method for healing in the future, and of course, a wide reception and a wide cover in pain units.

3. Low back pain (LBP) is a major public health issue. A thorough understanding of the pathophysiology and clinical manifestations is necessary to focusing a solid treatment.

4. In the management of the intervertebral disc disease (IDD), there are three headings: (1) Relief of pain by conservative management (physiotherapy, oral analgesia and supplements, alternative medicine); (2) Restorative treatment of the intervertebral disc (growth factor therapy, molecular or cell therapy) according to the principles of tissue engineering, (3) Surgery (decompression or total disc replacement, or rigid fusion surgery when necessary). With this in mind, the approach to IDD requires a multimodal technique in its management. Unfortunately, most conservative therapies and spinal surgeries are only aimed to relieve the symptoms, but do not address the cause of the degeneration. Even more, surgery techniques could accelerate the degeneration of adjacent segments.

5. Tissue regeneration strategies such as tissue engineering, growth factor administration, and stem cell-based therapies, have undergone significant development over the past two decades. Regenerative medicine, from tissue engineering to cell therapy, offers valuable treatment options, but sadly, they are rarely considered in daily clinical settings.

6. Growth factors have been enjoying more popularity in the field of regeneration of IDD and many have been proved to be effective in reversing the degenerative trend of the intervertebral disc. In this point, the epidural space is, in our opinion, the best option to perform this technique, as using this route -the

epidural space- will allow an effective activity on the disc, but also over the facet joints, and on the ligamentum flavum. Its antineuroinflammatory activity would relieve the associated neuropathic pain.

7. Finally, in IDD, the regenerative medicine option, such as the use of mesenchymal stem cells or platelet-rich plasma, has shown preclinical and clinical positive results. However, additional more powered high-quality studies are needed to really appreciate the long-term safety and efficacy of this technique approaches in the IDD process.

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