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The Effect of Administering Platelet Rich Plasma in Cases of Intervertebral Disc Degeneration

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Abstract

Introduction: Intervertebral disc (IVD) degeneration is a significant contributor to persistent back pain, with the IVD serving a vital mechanical role in weight transfer, energy dissipation, and joint mobility. The nucleus pulposus and annulus fibrosus work together to distribute and transmit loads between vertebral bones. Platelet-rich plasma (PRP), containing various growth factors, has gained attention due to its potential in clinical settings for stimulating cell growth and proliferation. This study explores the potential of autologous PRP therapy for improving degenerating IVD.

Objectives: The objective of this study is to assess the effectiveness of autologous PRP therapy in improving degenerating IVD based on clinical and histological features.

Methods: The author conducted an evidence acquisition process by analyzing and synthesizing information from various references. We used "intervertebral disc degeneration" and "platelet-rich plasma" as keywords to search for relevant literature on PubMed, Google Scholar, ProQuest, and Clinical Key. The data for this study were extracted from a total of 10 articles, comprising 6 experimental studies and 4 clinical trial studies.

Results: The study findings reveal that autologous PRP therapy induces significant improvements in degenerating IVD based on both clinical and histological features.

Conclusions: This study suggests that autologous PRP therapy is an effective approach for enhancing degenerating IVD, as evidenced by improvements in clinical and histological features. This research underscores the potential of PRP as a valuable technique in the clinical setting for addressing IVD degeneration and its associated back pain.

Keywords: Caspase, IVD, Nucleus Pulposus, PRP.

1. Introduction

One of the most debilitating medical conditions, intervertebral disc (IVD) degeneration is regarded as a key contributor to persistent back pain. Intervertebral discs are fibrocartilaginous tissues that lie between the vertebrae. IVD disease is caused by various causes such as aging, incorrect body posture, physical trauma, or genetic factors. Structural changes and degeneration of IVD lead to a variety of pain and other symptoms. With increasing age, the incidence of IVD disease increases. This occurs in 10% of the population at the age of 50 years to 50% at the age of 70 years. In some reports, degenerative disease of the intervertebral disc can be found in 90% of people; and many of them have no symptoms of the disease (Teraguchi et al., 2014).

Loss of cells in the nucleus pulposus (NP), results in an imbalance between synthesis and degradation of extracellular matrix (ECM), especially proteoglycans which play an important role in maintaining IVD hydration, and is considered one of the main causes of intervertebral disc (IVD) degeneration. Abnormal expression of growth factors (e.g., TGF β and IGF) and proinflammatory cytokines (e.g., IL-1 and TNF α) is also associated with degenerative processes. These changes ultimately compromise the anatomical and mechanical properties of IVD resulting in loss of disc thickness, disc deformation, and load-induced spinal deformity (Kushchayev et al., 2018).

Platelets are a constituent of blood cells which have potent regenerative cell properties. This is because it is rich in growth factors (Langer & Gawaz, 2008). It is known that growth factors can trigger collagen production, cell mitosis, angiogenesis, osteogenesis, cell differentiation, and stimulate stem cells to move towards the injury site to accelerate cell regeneration. These platelets are processed through a centrifuge machine to become platelet rich plasma (PRP) which is currently widely used as a natural source of growth factors in cell regeneration and soft tissue healing. Therefore, this study wanted to observe the effectiveness of PRP administration in improving intervertebral disc degeneration in experimental animals.

2. Theoretical Basis

Structure and Function of Intervertebral Discs

The spine is the pillar of our body and has three main functions, namely, to provide structural support, enable body movement, and protect the nervous elements. From a biomechanical point of view, the spine is a multiarticular structure consisting of many segments or units that allow multidirectional movement and absorption of large complex loads. The two adjacent vertebrae, the intervertebral disc, the spinal ligaments, and the facet joints between them constitute the functional spinal unit (FSU) representing the smallest motion segment of the spine and exhibiting biomechanical characteristics similar to those of the entire spine. Approximately 70% of the applied axial compression is transmitted by the vertebral bodies and intervertebral discs, with the remaining 30% of the load distributed through the facet joints (Kushchayev et al., 2018).

The intervertebral disc is a highly organized matrix. The central gelatinous part of the nucleus pulposus contains more collagen laterally and cartilage inferiorly and superiorly. In early life, some vascular supply is present in the end plate and annulus fibrosus, but blood supply recedes soon after birth. In the embryonic period, the axial skeleton originates from the sclerotome of the somites. The cells of the nucleus pulposus are initially of notochordal origin, but as they mature, they are replaced by chondrocyte-like cells that are thought to arise from the cartilaginous end plate. The nucleus pulposus is the central part of the disc, is hypoxic and relatively acidic. The nucleus pulposus contains aggrecan proteoglycans bound along hyaluronan chains. In a healthy, normal lumbar disc, the proteoglycans aggrecan and versican constitute the largest percentage of the dry weight of the nucleus. The glycosaminoglycan molecules both keratan sulfate and chondroitin sulfate fill the core proteins of aggrecan and versican and have a very high negative charge. This creates a hydrophilic matrix that attracts H20 molecules and provides pressure to resist axial loads against the disc. The glycosaminoglycan chain portion of proteoglycans carries a negative charge and produces osmotic swelling pressure within the irregular meshwork of collagen II fibrils. The disc height will decrease at the end of each day (Boyer, 2014).

The most important function of the intervertebral disc is mechanical, namely transferring weight, dissipating energy and facilitating joint mobility. The structures of the nucleus pulposus and annulus fibrosus act synergistically to distribute and transmit loads between the vertebral bones. Hydrostatic pressure is generated in the nucleus pulposus when the disc is compressed, which is limited peripherally by the annulus fibrosus, producing circumferential tensile forces within the lamellar structure. The compressive load is also directly supported by the inner part of the annulus fibrosus which is rich in proteoglycans. The layered angular structure and nonlinear nature of the annulus fibrosus facilitate joint mobility and stability in a variety of modalities, including bending and rotation and combinations of both (Taher et al., 2012).

Platelet-Rich Plasma (PRP)

Platelet rich plasma can be defined as blood plasma that contains 1,000,000 platelets/ml with a volume of 5 ml of plasma. It is widely known that platelet-rich plasma contains seven types of growth factors, namely: PDGF-AA, PDGF-BB, PDGF-AB, TGF-β1, TGF-β2, VEGF, EGF. And in-vivo growth factor levels are maintained after making platelet-rich plasma. The concentration of platelets in platelet-rich plasma can increase eight times the level of platelets in the blood so that the levels of growth factors in platelet-rich plasma also increase eight times except IGF-1 (Crane & Everts, 2008).

Platelet rich plasma was first used in heart surgery by Ferrari et al. in 1987 as a component of autologous transfusion after open heart surgery. Now it is followed by many specialists such as in maxillofacial surgery, cosmetics, spine, orthopedics, and overall wound healing (Crane & Everts, 2008).

Recently, PRP has received attention as a beneficial technique, primarily because of its autologous potential in the clinical setting. PRP contains biological growth factors that are able to stimulate cell growth and proliferation. In vitro experiments have shown that PRP can effectively promote animal intervertebral disc cell proliferation and ECM metabolism. Animal models have been recruited for experimentation, and artificially degenerated discs in a rabbit annular needling model are considered a satisfactory material to demonstrate the healing effect of PRP. There are most promising results, but questions about the evolution of restoration through time, the role of PRP cytokines and the mode of injury and injection remain (Gelalis et al., 2019).

The use of PRP has been considered a favorable technique for disc restoration, more promising than other techniques using purified growth factors, primarily because PRP can be isolated from autologous sources, thereby eliminating the concern of immune reactions (Gelalis et al., 2019).

In any case, the restoration process appears to be time-consuming, and models should probably include a longer duration of follow-up. Another limitation present in all animal studies is the degree of vertical loading of the spine in the upright model; the effects of PRP may not be as noticeable as the power on disk enhancement. Research by Gelalis et al. (2019) supported previous findings that discs treated with PRP directly retained their basic morphological characteristics, increased their cellularity, and preserved matrix metabolism. Moreover, our results show that early PRP injection is able to inhibit intervertebral disc degeneration (Gelalis et al., 2019).

The PRP dose given varied in several studies. Giving a dose of 0.2 cc in research conducted by Gelalis in 2019 is the dose commonly used. In another study, a dose of 20 µL of autologous PRP was also used in rabbits (Akeda et al., 2019). However, the results of the two doses have not been compared.

Caspase

Caspase is a protease, an enzyme that catalyzes the breakdown of proteins and is part of the cysteine-aspartic acid protease family. This substance is vital in the programming mechanisms of cell death in animals (apoptosis, pyroptosis and necroptosis), and also has an important role in inflammation. Due to its involvement in the regulation of cell death and inflammation, caspase activity is essential for regulating homeostasis in the body (McIlwain et al., 2013).

In mammals, there are three types of caspases that have their own roles. Two of them are involved in apoptosis: the initiator caspase which starts apoptosis, while the executioner caspase which processes protein breakdown which is also known as the proteolysis process. The third caspase, inflammatory caspase, is vital for signalling inflammatory cytokines along with various other cell deaths (McIlwain et al., 2013).

In recent years there has been a rapid development of new information on the molecular mechanisms that control caspase activity. These studies are important because they allow researchers to formulate new ways to modulate the dysfunctional cell death and inflammatory pathways that are characteristic of various inflammatory, malignant, metabolic and neurodegenerative diseases (McIlwain et al., 2013).

3. Methods

This article was conducted by analysis and synthesis from various references. The authors use “intervertebral disc degeneration” and “platelet-rich plasma” as keywords to explore the literature from PubMed, Google Scholar, pro-Quest, and clinical Key. The related papers published in the last fifteen years were included, while non-full-text papers were excluded. these papers were analyzed subsequently to answer the aim of this study.

A total of 10 articles were selected for data extraction and analysis. Among these, 6 articles presented experimental studies, while the remaining 4 articles focused on clinical trials. This diverse selection of research articles forms the basis for the findings and conclusions of this study, providing a well-rounded perspective on the effectiveness of platelet-rich plasma in addressing intervertebral disc degeneration.

4. Results

The intervertebral disc (IVD) is essential for spinal function, providing support, enabling movement, and protecting nerves. It's a complex structure, with the nucleus pulposus in the center and the annulus fibrosus surrounding it. IVD degeneration involves changes in these structures, leading to reduced hydration and mechanical function. Patients with degenerative discs experience pain, radicular symptoms, and weakness. Platelet-rich plasma (PRP) therapy, containing growth factors, shows promise in inhibiting degeneration and promoting healing. Caspase, an enzyme involved in cell death and inflammation regulation, plays a crucial role in maintaining body balance. Understanding caspase activity is important for addressing various diseases. In summary, this research underscores IVD's importance, its degeneration process, clinical symptoms, and the potential of PRP and caspase-related therapies. Surgery is an option for severe cases with failed non-surgical treatments.

Clinical Manifestation

Patients with degenerative discs often present with many symptoms including pain, radicular symptoms, and weakness. LBP can be made worse by position and movement. Flexion often worsens symptoms, while extension will relieve them. Increased pain with extension may indicate facet arthropathy. When examining patients with suspected degenerative lumbar discs, it is important to rule out other known etiologist for their pain. Abdominal abnormalities including aortic aneurysm, pancreatic disease, and kidney stones must be excluded. Additionally, it is important for patients to be asked about other symptoms such as fever, chills, fatigue, and weight loss, which may be indicative of other pathologies (Smith et al., 2011).

Pathogenesis of Intervertebral Disc Degeneration

The phases during the degeneration process consist of significant changes in the nucleus pulposus, annulus fibrosus, and barrier function. Significant changes in the nucleus pulposus occur at various levels. At the cellular level, there is a transition from notochordal to chondrocyte to fibro chondrocyte cell types. Extracellular matrix alterations involve a decrease in aggrecan type and an increase in type I and II collagen. On a tissue level, the transition from liquid viscoelastic to solid viscoelastic occurs, accompanied by mechanical changes, including a decrease in hydrostatic pressure, which becomes more heterogeneous. Significant changes in the annulus fibrosus also manifest at different levels. At the cellular level, fibro chondrocytes (inner) and fibroblasts (outer) undergo a transformation into uniformly fibro chondrocyte cells. Changes in the extracellular matrix involve a reduction in type 2 collagen (from the inside to the outside) and an increase in type 1 collagen. At the tissue level, the lamellar structures disappear, giving way to a fibrocartilaginous composition. Mechanical changes encompass lamellar stretching and radial compression, resulting in unified axial compression.

Regarding barrier function, at the cellular level, there is cytokine secretion and infiltration of inflammatory cells and immune cells. Changes in the extracellular matrix take the form of further degradation of collagen and proteoglycans. On a tissue level, there is the growth of vascular and neuronal structures. With advancing age, alterations in the composition of the disc extracellular matrix, along with reduced aggrecan content in the nucleus pulposus, lead to decreased hydration, ultimately impairing mechanical function. The less hydrated and more fibrous nucleus pulposus struggles to evenly distribute pressure between the vertebral bodies, causing uneven

pressure transfer around the annulus fibrosus. These changes affect its mechanical properties, resulting in progressive structural deterioration, including circumferential and radial tears. In some cases, injuries may progress into a posterior radial bulge or herniation of the nucleus pulposus material, leading to complaints of severe pain. A decreased thickness of the nucleus pulposus is typically associated with advanced disc degeneration and can be observed as tenderness in surrounding structures on MRI images (Taher et al., 2012).

5. Discussion

Management of IVD Degeneration with PRP

Recently, PRP has received attention as a beneficial technique, primarily because of its autologous potential in the clinical setting. PRP contains biological growth factors that are able to stimulate cell growth and proliferation. In vitro experiments have shown that PRP can effectively promote animal intervertebral disc cell proliferation and ECM metabolism. Animal models have been recruited for experimentation, and artificially degenerated discs in a rabbit annular needling model are considered a satisfactory material to demonstrate the healing effect of PRP. There are most promising results, but questions about the evolution of restoration through time, the role of PRP cytokines and the mode of injury and injection remain (Gelalis et al., 2019).

The use of PRP has been considered a favorable technique for disc restoration, more promising than other techniques using purified growth factors, primarily because PRP can be isolated from autologous sources, thereby eliminating the concern of immune reactions (Gelalis et al., 2019). In any case, the restoration process appears to be time consuming, and models should probably include a longer duration of follow-up. Another limitation present in all animal studies is the degree of vertical loading of the spine in the upright model; the effects of PRP may not be as noticeable as the power on disk enhancement. Research by Gelalis et al. (2019) supported previous findings that discs treated with PRP directly retained their basic morphological characteristics, increased their cellularity and preserved matrix metabolism. Moreover, our results show that early PRP injection is able to inhibit intervertebral disc degeneration (Gelalis et al., 2019).

Chai et al showed that PRP/FA-rich hydrogel combination performs an active function in stimulating extracellular matrix production, strengthening and healing degenerative intervertebral discs in rats (Chai et al., 2023). In another study by Cheng et al, at 5–9 years after the PRP injection, patients showed statistically and clinically substantial improvements in pain and function (Cheng et al., 2019). Both in vitro and animal investigations have demonstrated that platelet-rich plasma has a favorable influence on the extracellular matrix of the intervertebral disc. In experimental study by Yang et al, showed that the TGF-b1/Smad2/3 pathway may be crucial to PRP's capacity to delay the degeneration of the intervertebral disc (Yang et al., 2016). Levi et al also performed a trial on patients with chronic discogenic low back pain. Two months after 1,5 mL WBC-rich PRP injection, 41% of 22 patient achieved a 50% decrease in VAS (Levi et al., 2016). Another study by Hussein showed that weekly routine of PLRP injection for six weeks can relieving chronic low back pain and disability with long-term patient satisfaction and success rate of 71.2% (Hussein & Hussein, 2016). Lutz et al suggest that employing PRP preparations with a higher percentage of platelets can improve clinical results (Lutz et al., 2022). Effect of autologous PRP on intervertebral disc degeneration that studied by Obata et al in the Rabbit showed that PRP is effective in restoring disc height and increasing chondrocytic cells in the IVD of the rabbit annular puncture disc degeneration model (Obata et al., 2012). In other experimental study by Ma et al found that PRP give more regenerative effect in restoring intervertebral disc while combined with adipose tissue-derived stromal cells (ADSCs) (Ma et al., 2019). Another PRP combination was observed by Hou et al on rabbit IVD, and the result showed that the BMP2-transduced BMSCs and PRP gel can significantly promote the repair of the degenerated discs in vivo (Hou et al., 2016). The summary of 10 articles is in Table 1.

The PRP dose given varied in several studies. Giving a dose of 0.2 cc in research conducted by Gelalis in 2019 is the dose commonly used. In another study, a dose of 20 µL of autologous PRP was also used in rabbits (Akeda et al., 2019). Cheng et al use 3–4 ml of leukocyte-rich PRP to treat low back pain patient (Cheng et al., 2019). However, the results between the doses have not been compared.

Surgery is indicated in cases of severe and progressive neurological deficit or pain with failed non-surgical therapy for 6-12 weeks. Indications for surgery include progressive cervical radiculopathy, persistent radicular symptoms after 4 to 8 weeks of treatment without surgery, instability with radicular symptoms, and motor deficits (Truumees & Prather, 2021).

Table 1: Recent PRP Studies in Vivo

No	Study	Year	Agent	Target	Sample Size	Injection site	Follow up period	Result
1	Gelalis et al (2019)	2018	0.2 cc PRP	Rabbit	18	Lumbal	6w	Degeneration was significantly lower in PRP group
2	Chai et al (2023)	2023	1.6% Hyaluronic Acid + PRP + Ferulic Acid	Rat	45	Lumbal	8w	hydrogel/PRP/FA has a good effect on degenerative intervertebral disc
3	Cheng et al (2019)	2019	3–4 ml of leukocyte-rich PRP	Human	29	Lumbal	5-9y	there were statistically significant improvements in pain and function($p<0.001$).
4	Yang et al (2016)	2016	15 μL of PRP + 10 μL of TGF-bl inhibitor	Rabbit	24	Lumbal	12w	the PRP plus inhibitor injection group had significantly lower expression levels of Smad2/3 and collagen II than the PRP group
5	Levi et al (2016)	2016	1.5 mL WBC rich PRP	Human	22	Lumbal	6m	at 1 months, 36% achieved a 50% decrease in VAS independent of their ODI score at 2 months, 41% achieved a 50% decrease in VAS independent of their ODI score at 6 months, 9/19 patient 50% decrease in VAS
6	Hussein M and Hussein T (2016)	2016	weekly PLRP injection for six weeks	Human	104	Lumbal	24m	Relieving chronic low back pain and dissability with long-term patient satisfaction and success rate of 71.2%
7	Lutz et al (2022)	2022	2ml PRP per disc	Human	37	Lumbal	18.3 ± 13.3 m	Significant improvements in pain and FRI scores

8	Obata et al (2012)	2012	one injection of PRP (20 μL) and one injection of PPP (20 μL)	Rabbit	12	Lumbal	12w	effective in restoring disc height and increasing chondrocytic cells in the IVD of the rabbit anular puncture disc degeneration model
9	Ma et al (2019)	2018	200 μL PRP	Rabbit	5	Lumbal	4w	PRP-combined ADSCs had the most effect in restoring the intervertebral disc
10	Hou et al (2016)	2015	40 μL of BMP2-transduced BMSCs and PRP gel	Rabbit	60	Lumbal	12w	BMP2-transduced BMSCs and PRP gel can significantly promote repair of the degenerated discs in vivo

6. Conclusion

Autologous Platelet-Rich Plasma (PRP) therapy has demonstrated remarkable efficacy in ameliorating intervertebral disc (IVD) degeneration, as evidenced by substantial improvements in both clinical and histological characteristics. This therapeutic approach holds great promise for patients suffering from IVD degeneration, offering a potential solution to alleviate their pain and discomfort while promoting structural restoration and enhanced disc function. The clinical benefits of autologous PRP therapy are underscored by its ability to enhance patients' overall well-being, providing relief from the debilitating symptoms associated with IVD degeneration. Furthermore, histological assessments reveal positive changes within the disc's cellular and structural components, suggesting a regenerative effect of PRP therapy. These combined clinical and histological findings strongly support the use of autologous PRP as a viable and effective treatment option for individuals grappling with the challenges posed by degenerating intervertebral discs.

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