Platelet-rich Plasma for Spine Conditions: A review of Published Research

Abstract
Regenerative medicine is a field of medicine that uses the body’s ability in healing the tissues or damaged body parts. This area is extensively used in orthopedics, specifically in the treatment of disc destructive diseases, as well as injuries and inflammation of the tendons, joints, and ligaments. The most commonly used product in this field is platelet-rich plasma (PRP). In this research, we reviewed human clinical studies conducted to evaluate the role of PRP in spinal diseases.

Keywords: Platelet Rich Plasma, Bone Fusion, Disc

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Platelet Structure
Platelets are about 1-3 μm in size with a half-life of seven days and physiological numbers are from 150,000 to 400,000 per μL of blood cells. The main source of these cells is bone marrow megakaryocytes and contain microtubules (cytoskeleton), glycogen, lysosomes, serotonin, calcium, dense granules (including ADP, ATP, and serotonin granules, and calcium). The main source of these cells is bone marrow megakaryocytes and contain microtubules (cytoskeleton), glycogen, lysosomes, serotonin, calcium, dense granules (including ADP, ATP, and serotonin granules, and calcium). Granule a in platelets includes coagulation factors, growth factors and other proteins. The main role of these factors in homeostasis is wound and bone healing.
Almost every platelet contains 50 to 80 granules. Over the past few years, the role of growth factors and platelet cytokines in angiogenesis, cell production and proliferation, stem cell migration, inflammation and stimulation of extracellular matrix synthesis has been recognized. Wound healing is initiated with the accumulation of platelets and the release of platelet growth factors, and PGF plays a key role in different healing stages. Therefore, PGFs are used locally to heal the wound of different surgeries, including orthopedic surgeries. Apart from the role of platelets for surgical wound healing, platelet plays a prominent role in orthopedic surgeries due to their direct effect on bone healing and stimulation.

The Role of Platelet Growth Factors in Bone Repair

Bone is one of the connective tissues that contains various cells and a strong bone scaffold. Bone cells include osteoclasts, osteoblasts, osteocytes, osteogenic cells, and hematopoietic cells. The process of bone healing in cases of osteoblast fractures and bone injury begins with the secretion of various growth factors found in the platelets. In primary stages of a fracture, platelets aggregated at the site of injury play a role in callus formation by secreting various growth factors, including PDGF, TGF-B, and EGF. In this regard, TGF-beta is primarily responsible for the bone healing process, the receptor of which is on chondrocytes and osteoblasts. In addition, bone induction of stem cells to mature bone cells occurs in the presence of growth factors including PDGF and TGF beta. Different types of PRP include:

1. Pure platelet-rich plasma: this product is leukocyte-free and has a network of fibrin in addition to platelet concentrate. Used in gel or liquid form, the product has a plasma concentration of three-eight times the blood volume.
2. Leukocyte and platelet-rich plasma (L-PRP): in addition to platelet concentrate, there are also leukocytes and a network of fibrin.
3. Pure platelet-rich fibrin (P-PRF): this is a product of leukocyte-free platelet concentrate with a high concentration of fibrin in the form of a gel.
4. Leukocyte and platelet-rich fibrin (L-PRF): leukocyte along with a high fibrin concentration in the form of a gel.

In the next section, we review the articles published in the field of the role of PRP in the treatment of spinal diseases and surgeries. Role of PRP in Chronic Low Back

Generally speaking, 80% of people experience low back pain in their lifetime. Pathologic origin of spine pain can be from ligaments,
muscles, sacroiliac joint, fast, and disc. In this regard, various studies have evaluated the effect of PRP on the mentioned factors, as shown below.

**Spinal Muscular Atrophy**

Paraspinal muscles play a key role in spinal stability. Atrophy of these muscles with degenerative disk diseases is the most common cause of chronic low back pain. In this regard, a common treatment is paravertebral corticosteroid injection, which is associated with several complications and decreases pain for a short period (13). In a research, Hussein (2016) evaluated the effect of platelet-leukocyte-rich plasma injection in atrophic multifidus muscle on 115 patients with chronic low back pain for the first time. Injections were carried out weekly for six weeks. From 50 ml of blood, 2.5 ccs of platelet-rich plasma was obtained, and patients were assessed using the numeric pain scale (NPS), Oswestry disability index (ODI) and evaluating patient satisfaction, modified MacNab, and a lumbar MRI. According to the results, ODI decreased by 45% and NPS was reduced from 8.8 to 3.4. In addition, FATTY changes decreased by 87.8% in the MRI of patients one year later. A two-year follow-up of the patients demonstrated that 71.2% of individuals were satisfied with their treatment and Mod.Macnab was reported excellent and good in 60% and 17% of the subjects, respectively (13).

**Sacroiliac Joint**

Overall, 20% of low back pain is related to the inflammation of the sacroiliac joint (SI joint). In a study (2017) on four patients with SI joint inflammation, injection of two ccs of platelet-rich plasma was performed under ultrasound guidance. In addition, ODI, NRS and short McGill pain questionnaire were evaluated. 12 months after the injection, there was a significant improvement in joint stability, pain relief and increased life quality in patients. The results were continuous and satisfactory after four years (14). In a study (2016), 40 patients with SI joint inflammation were divided into two patient and control groups, where the subjects in the former group received intra-articular injection of three ccs of PRP and the participants in the latter group received intra-articular injection of 1.5 ccs of methylprednisolone, 1.5 ccs of lidocaine, and 0.5 ccs of normal saline under ultrasound guidance. In the mentioned study, the scores of VAS modified Oswestry Disability Questionnaire (MODQ), and short-form health survey (SF-12) were assessed in the second, fourth, and sixth weeks and the three months after the injection. According to the results, a significant difference was observed between the two groups in the sixth week and the third month after the intervention. Moreover, while MODQ and SF-12 scores considerably improved in the case group in the fourth week and the third month, there was an improvement in the control group in the fourth week but the patients’ condition deteriorated in the third month. In the aforementioned study, the intervention effectiveness was 90% and 25% on the PRP and control groups, respectively (15).

**Facet Mediated Pain**

Lumbar facet joint syndrome is responsible for chronic low back pain in 15-52% of patients. In addition, facet joint syndrome occurs due to capsule elongation, entrapment of the nerve by osteophytes, and release of inflammatory compounds. In addition, degenerative changes and osteoarthritis lead to facet mediated joint syndrome. Various treatments are used for this condition, including radiofrequency and topical injections of steroids and anesthetics. In a study, Wu et al. (2016) evaluated the effect of intra-articular injection of PRP to 19 patients with a lumbar facet joint. These scholars used the Roland-Morris disability questionnaire (RMQ), visual analog scale (VAS) at rest and during flexion, ODI, and modified MacNab in the first week and three consecutive weeks after injection. The ODI results were indicative of 10% improvement and excellent outcomes for 47% of patients immediately after injection, 74% of patients in
the first week, and 79% in the first, second and third months \(^{(16)}\).

In another study by Wu (2017), 46 patients were divided into two groups of 21 (PRP) and 23 (corticosteroids with anesthetics). The patients were injected with 0.5 ccs of PRP and were evaluated one week, as well as one, two, three and six months after the injection using VAS at rest and during flexion, ODI, and RMQ. According to the results, there was a significant difference between the test and control groups regarding VAS, ODI, and EMQ. According to MacNab criteria, 80% improvement was achieved in the PRP group after one month while only 50% improvement was reported for the control group \(^{(17)}\).

**Radiculopathy**

The spinal nerves exit the lamina beyond the neural foramen and cause chronic lumbar pain in cases of inflammation and congestion. The most common treatment for these pains is the injection of anesthesia and epidural steroids. The PRP contains various anti-inflammatory proteins such as interleukin receptor antagonist, alpha-2-macroglobulin and metalloproteinase inhibitor that can help control the inflammation of radiculopathies \(^{(18)}\). In a study by Centeno (2017), intra or transforaminal injection of PRP was carried out and numeric pain score (NPS), functional rating index (FRI), and a modified single assessment numeric evaluation (SANE) rating were applied to collect data. According to the results, NPS and FRI significantly changed in the first, third, sixth, 12th, 18th, and 24th months, and there was a 50% improvement by the end of the 24th month based on the average modified SANE.

**Discogenic Disease**

In total, 40% of chronic low back pains are due to the destruction of intervertebral discs, which are the largest body part that has no vessels and only contains a few small branches of metaphysical vessels around the external annulus, which leads to their low ability to heal annulus injuries and ruptures. Intervertebral disc contains nucleus pulposus at center consisting of collagen 2 and hydrophilic proteoglycan, and the peripheral portion of the annulus is fibrosis, which contains collagen I. With repeated strokes, annulus fibrosus causes cystic changes, nucleus pulposus is dehydrated and experiences fibrotic changes and necrosis, and comes out of annular fissures. Spontaneous recovery occurs in 38% of the cases. However, the main cause of pain in patients is the lack of improvement in the status of torn annular fissures. Increased IL-1 and TNF alpha cytokines stimulate area nerves and releases degeneration enzymes, and more mediators into the epidural space. The disc height decreases gradually and leads to spinal stenosis and deformities. Various studies have shown that changes in the process of disk degeneration include the decrease of proteoglycans, collagen fibers and fibronectin and changes in the nutrition pathways, the main cause of which is the release of different inflammatory factors such as types of interleukins, interferon-gamma, and TNF alpha during inflammation and injury \(^{(19)}\). To prevent injury, more emphasis should be placed on extracellular matrix production, inhibition of inflammatory cytokine production, and inhibition of matrix degeneration enzymes. To prevent injury, more emphasis should be put on extracellular matrix production, inhibition of inflammatory cytokine production, and inhibition of matrix degeneration enzymes \(^{(20)}\). The role of PRP in the treatment of discogenic diseases through the decrease of apoptosis, an increase of proteoglycan synthesis, annulus cell proliferation, inhibition of the inflammatory effect of TNF alpha, and interleukin-1 has been shown in animal studies \(^{(20)}\). In a study by Akeda (2011), 2 ccs of disc PRP was injected to six patients, who were followed up for six months in terms of using VAS, Rolland-Morris disability questionnaire, as well as radiography and MRI. In the end, 50% pain reduction and 80% decrease in RDQ one and six months after the injection were reported, while MRI showed no change \(^{(21)}\). In a study (2015), six patients with discogenic pain
were injected with two ccs of PRP inside nucleus pulposus and were followed up for 24 weeks. According to the results, the verbal pain scale score of the subjects decreased by more than 50%. In addition, MRI showed positive changes in a few patients (22). In a study, Tukali (2016) assessed 47 patients with chronic discogenic pain divided into two test and control groups of 29. In this study, the participants received four ccs of PRP in the middle part of the disc using a 25 gauge needle, and their functional rating scale (FRI) and 36-item short-form health survey (SF-36) scores were assessed after eight weeks. Lack of complications and improvement were observed in the subjects of the test group regarding pain, performance, and patient satisfaction, compared to the control group (23).

In a study in 2015 by LEVI, 22 patients were injected with two ccs of PRP, and the VAS and ODI scores were evaluated after six months of follow up. According to the results, there was a 50% and 30% decrease in VAS and ODI scores, respectively, and improvement was observed in 14% patients after one month, 32% patients after two months, and 47% of patients after six months (19). In another research in 2016, 10 patients were injected with five ccs of intra-laminar PRP and their VAS, SLRT (straight leg raising test), and MODQ (modified Oswestry disability questionnaire) scores were assessed after three months. In the end, the MODQ score of all patients was below 30% and their SLRT was above 70 (24). In a research in 2017, one patient was followed up via an MRI 12 months after receiving a one-two-cc dose of PRP. The MRI results showed an increase in T2 signal intensity (25). In another study by Akeda (2017), 14 patients were injected with two cc PRP at the desired level, and the mean follow-up duration was 10 months. After one month, the VAS score decreased by 50% and remained low for six-12 months. However, there was no change in the level of T2 (26).

There are various injection approaches to treat low back pain. In this regard, different studies can use epidural and intra-articular injections (except for intradiscal injection) to treat discopathy. In a research by Kirchner (2018), 86 patients received PRP (four ccs in the disc and two ccs in the facet) by intradiscal, intraarticular, and epidural injections. After six months, the VAS scores of the patients demonstrated a significant decrease in this respect. In addition, the results of 91% of the patients were reported excellent (27). Discogenic surgeries have a mortality rate of about 0.1-0.6% despite rare complications. In addition to the complications, the superiority of surgery to conservative treatments is unclear (28). Most of the studies mentioned are level two and three clinical cases, and lack of a control group and not being a retrospective study are their major weaknesses that can be corrected in future studies.

**Role of PRP in Spinal Fusion**

Discogenic surgeries have a mortality rate of about 0.1-0.6% despite rare complications. In addition to the complications, the superiority of surgery to conservative treatments is unclear (28). The bone graft is the gold standard in lumbar fusions regardless of concerns about donor bone deficiency. Iliac crest, growth factors, allograft, demineralized bone matrix, and ceramic are extensively applied for the bone graft. Recently, various clinical studies have evaluated the role of PGFs in spinal fusion. The clinical studies conducted on this topic and published in the past 10 years are assessed and shown in Table 1. In a study in 2007, 50 patients with cervical disc herniation received cervical fusion with allograft and fixation, and platelet gel was applied during surgery. After 52 weeks, the participants were evaluated in terms of radiography results, VAS score, and neck disability index. According to the results, premature fusion was reported in patients treated with platelet gel at week 12, and 84% of fusion was observed in the platelet gel injection group (29).
In 2009, 67 patients were treated with posterior spinal fusion. In addition, 34 patients received platelet gel treatment. Two years later, the evaluation of the patients with CT scans and radiography showed that the platelet gel had no effect on bone fusion level \(^{(30)}\). In a research in 2010, 15 patients with the spinal injury in the thoracic and lumbar region underwent an anterior and posterior fusion with PRP. After assessing the patients with CT scan and VAS score, no significant difference was observed between the groups regarding the latter variable. In addition, CT scan results revealed no significant increase in bone density in the PRP group, compared to the control group \(^{(31)}\). In a research by Sys et al. (2011), 38 patients in two case groups received posterior spinal fusion with iliac crest and PRP while the subjects in the control group did not receive PRP injections. The participants were assessed on the 3rd, 6th, 12th, and 24th post-operative months via CT scan and radiography and in terms of VAS, ODI and SF-36 scores. In the end, no difference was observed between the groups in terms of VAS and ODI scores and the CT scan results showed incomplete bone healing in both groups, and no difference was observed between the groups. According to the results of the mentioned study, no considerable difference was observed between the PRP treatment and no treatment groups. However, the inhibitory effect on bone fusion was not observed during the treatment process \(^{(32)}\).

Cortina (2011) conducted a study on 107 patients with lumbar degenerative disease. In this study, 67 patients were treated with autograft treatment with PRP, hydroxyapatite and tricalcium phosphate. In the control group, 40 patients underwent surgery without PRP injection. After 24 months of follow-up, radiography results showed that PRP reduced fusion rates \(^{(33)}\). In 2012, Sheth assessed the effect of PRP on orthopedic injuries in a meta-analysis (2012). In addition, 22 trial studies and 10 cohort researches were evaluated, and the results were indicative of no apparent difference between PRP and control groups regarding spinal surgeries \(^{(9)}\). In 2014, Tarantino assessed 22 patients by implanting a cancellous substitute along with PRP on one side and cancellous substitute fusion along with saline on the other side. Six and 12 months after the surgery, the CT scan results were indicative of a significant increase in bone density of the participants six months.
after the surgery, compared to the control group.\textsuperscript{(34)}

In a study by Vadala (2016) on 10 patients with a one-year follow-up and CT scan, the combination of PRP and bone marrow concentrate along with thrombin in one side of the patient and independent use of allograft in the other side of the patient showed an increase in bone fusion with PRP and bone marrow concentrate.\textsuperscript{(37)} In a study in 2017, researchers evaluated the effect of PRP on two groups of 20 patients undergoing bone fusion surgery. In this study, the researchers applied two different methods to retrieve PRP; one method included patients’ venous blood while the other method required blood inside the surgical field to produce PRP. ELISA was used to evaluate PDGF and TGF beta in two PRP samples prepared. According to the results, no difference was observed between the two PRP samples in terms of the number of growth factors. In addition, evaluation of the cellular proliferation in HBMSCs (human bone marrow-derived mesenchymal stem cells) demonstrated a lack of difference between the groups while both types of PRP stimulated cellular production, compared to the control group.\textsuperscript{(38)}

In a study by Imagama (2017) on 29 patients undergoing spinal fusion surgery due to lumbar degenerative disease in level I4-I5, the researchers conducted an independent bone graft on the left side of the patients and along with PRP in the right side of the patients. In the end, the level of bone fusion was assessed via CT scan in the 2nd, 3rd, 6th, and 12th postoperative months. The Japanese Association Score was indicative of 79% improvement in the case group. According to the comparison of 58 regions in CT scan in the 2nd, 3rd and 6th months, the level of fusion was apparently higher in the PRP group. However, the two groups were homogenous in terms of the fusion level after 12 months. In addition, comparison of the groups regarding the bone resorption rate revealed a lower level in the PRP group in the 2nd, 3rd, and 6th months, compared to the case group. 10 years later, the CT scan and radiography results demonstrated 100% fusion in the case group and no report of infection and excess bone formation.\textsuperscript{(35)} In a research by Kubota (2017) on 62 patients divided into case and control groups of 31, two ccs of PRP was injected during surgery, and the level of fusion and fusion mass size was assessed by radiography and CT scan every three months. In addition, the duration of fusion and clinical criteria of leg and back pain and leg numbness were assessed. The results were indicative of 94% and 74% bone fusion in the case and control groups, respectively. Moreover, fusion mass was reported at 572 vs. 367 mm in the case and control groups, respectively. Furthermore, time to reach fusion was approximately seven months in the control group and nine months in the control group, and there was no difference between the two groups in terms of clinical criteria.\textsuperscript{(36)}

In a study by Kubota (2018) on 22 patients, 11 of whom received fusion with PRP injection and two ccs of PRP was injected during surgery, radiography and CT scan results were assessed along with VAS score in the 12th and 24th months to evaluate fusion. In the PRP injection group, bone fusion was reported at 91%. Meanwhile, bone fusion was observed in 77% of cases of the control group. Nonetheless, the research groups were homogenous in terms of fusion time, and there was no difference between the patients regarding back and leg pain and leg numbness.\textsuperscript{(39)} It cannot be said that PRP is certainly involved in bone fusion due to the low sample size, lack of precise inclusion criteria, insufficient evidence, and methodological differences of studies.

Discussion and Conclusion

Results of different studies have shown the role of PRP in the treatment of spinal diseases. Some studies of discogenic disease with single-
and double-clinical evidence have shown the effect of intracervical injection of two ccs of PRP by reducing pain and clinical symptoms as well as disc signal changes on MRI. While a definite conclusion cannot be made due to differences in research and follow-ups with different time intervals, it seems that clinical impact initiates after six months and continues to 12 months. Today, the purpose of surgery of discogenic patients and those with other spinal diseases (e.g., canal stenosis and spondylolisthesis) is reducing complications and maximizing effectiveness. In this regard, the most common surgery is bone fusion, for which different methods and materials have been used by several studies to fasten and increase fusion. However, most studies conducted to evaluate the role of PRP in bone fusion surgery have had unsatisfactory results, and more studies on larger sample sizes and with longer follow-ups are required.

References

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