Platelet-Rich Plasma for the Treatment of Low Back Pain. Article review

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Abstract

Globally, back pain is a problem that costs a lot of money and causes a lot of impairment and disability. Present treatment approaches frequently offer suitable alleviation, but do not tackle the underlying causes. In degenerative disorders, the aim was to restore anatomical function by numerous regenerative cellular methods to alleviate lower back pain. Platelet-rich plasma (PRP) is made up of the large number of autologous platelets that are suspended in a limited plasma volume. Furthermore, PRP is prepared by the use of different modalities and could be administered by injection or applied topically. Whereas the mechanism of action is unknown, in *vivo* and *vitro* investigations have revealed cellular and biochemical alterations related to mechanical structure and inflammation. Using patient data and animal models, PRP injection research has revealed insight into chondroprotection, pain relief, and the factors which influence the therapeutic efficiency. PRP injection has lately been recommended in a few types of research as a fairly safe way to treat patients who have degenerative disc disease and failed to find other ways to manage their lower back pain. For the sacroiliac joint discomfort, PRP injections aren't an approved therapy option, and the evidences for their effectiveness is limited to small RCTs and case report studies. According to limited number of prospective studies, PRP injection might be beneficial in treating pain or functional decline resulting from facet joint arthropathy. For improving the evidence quality and evaluating the safety and efficacy of PRP injections for many prevalent causes of chronic back pain, more research is needed.

Keywords: Platelet-rich plasma. PRP. PRP injections. Chronic back pain

الخلاصة:

على الصعيد العالمي ، تعتبر آلام الظهر مشكلة تكلف الكثير من المال وتسبب الإعاقه والعجز. تقدم طرق العلاج الحالية في كثير من الأحيان تسكينًا مناسبًا ، ولكنها لا تعالج الأسباب الأساسية. في الاضطرابات التنكسية ، كان الهدف هو استعادة الوظيفة التشريحية من خلال تجديد الخلايا للتخفيف من آلام أسفل الظهر. تتكون البلازما الغنية بالصفائح الدموية من عدد كبير من الصفائح الدموية الذاتية المعلقة في حجم محدود من البلازما. علاوة على ذلك ، يتم تحضير البلازما الغنية بالصفائح الدموية بواسطة استخدام طرائق مختلفة ويمكن إعطاؤها عن طريق الحقن أو تطبيقها موضعياً. في حين أن آلية العمل غير معروفة ، كشفت التحقيقات في الجسم الحي والمختبر عن تغيرات خلوية وكيميائية حيوية تتعلق بالهيكل الميكانيكي والالتهاب. باستخدام بيانات المريض والنماذج الحيوانية ، كشفت أبحاث حقن البلازما الغنية بالصفائح الدموية عن نظرة ثاقبة لحماية الغضروف وتخفيف الآلام والعوامل التي تؤثر على الكفاءة العلاجية. تمت التوصية مؤخرًا بحقن البلازما في أنواع قليلة من الأبحاث كطريقة آمنة إلى حد ما لعلاج المرضى الذين يعانون من مرض القرص التنكسي وفشلوا في إيجاد طرق أخرى لعلاج آلام أسفل الظهر. بالنسبة لألم المفصل العجزي الحرقفي ، فإن حقن البلازما ليست خيارًا معتمدًا للعلاج ، وتقتصر الأدلة على فعاليتها على التجارب المعشاة ودراسات تقرير الحالة. وفقًا لعدد محدود من الدراسات المستقبلية ، قد يكون حقن البلازما الغنية بالصفائح الدموية مفيدًا في علاج الألم أو التدهور الوظيفي الناتج عن الاعتلال المفصلي الوجهي. لتحسين جودة الأدلة وتقييم سلامة وفعالية الحقن للعديد من الأسباب السائدة لآلام الظهر المزمنة ، هناك حاجة إلى مزيد من البحث.

1. Introduction

Back pain has been considered a rising condition that costs a lot of money and causes a lot of impairment all over the world. The worldwide prevalence of lower back pain is 9.40%, with a prevalence of 13.1% in the United States [1, 2]. The back pain had been indicated by around 59 million grown-ups in the United States, or 28% of the population [3] and nearly 65% of the people of the United Arab Emirates (UAE) [4] which was slightly higher than that of Toya technical institute staff (61.4%) in Kurdistan Region of Iraq [5]. Chronic low back pains are more common in specific populations, particularly those with poor education and income [1, 4, 5, 6]. Obesity, older age, cigarette smoking, depression, and other medical comorbidities have all been associated with a greater incidence of chronic lower back pain [1, 5, 7, 8].

Low back pain is becoming more widespread, and the associated expenses were estimated to reach $84 billion per year [9]. Chronic low back pain might limit physical activity, resulting in productivity loss and disability. Lower back pain ranks 6th in terms of disability-adjusted life years (DALY), with 12.8% of individuals in the United States receiving disability income [1, 9]. Back pain has been stated as the cause of job incapacity by 33% of 21 million people who report it [10]. Back pain patients miss an average of 5.2 hours of work each week [11, 12]. In addition, patients who have chronic pain generally limit their leisure activities and social interactions; also, they are (3-4) times more likely to have depression compared to the general population [13, 14].

In roughly 85% of cases, the origin of the low back pain is unknown. Yet, structural defects or injuries of ligaments, facet joints, blood vessels, vertebral periosteum, roots of the spinal nerves, and other structures have been identified as possible causes. The thinning of the central spinal canal or lateral recesses, which has been referred to as spinal stenosis, is one of the most common causes of back pain which is diagnosed only when symptoms of neurogenic claudication and/or cervical myelopathy are present. The symptomatic spinal narrowing can be congenital, or, more frequently, acquired.

The latter may be the result of systemic illnesses, namely endocrinopathies (such as Cushing disease or acromegaly), calcium metabolism disorders (including

hypoparathyroidism and Paget disease), inflammatory diseases (such as rheumatoid arthritis), and infectious diseases. [15]. The narrowing of the spinal column opening through which spinal nerves exit is known as neuroforaminal stenosis [16]. Also, symptoms might be caused by neuropathic low back pain, which is caused by aberrant neurologic pain [17]. Nociception is the process of sending information about tissue injury to the brain that has been modulated via specific receptors called nociceptors. In the case where the release of the inflammatory mediators is performed at the site of the original injury, nociceptor cells are stimulated, allowing afferent signals to be transmitted to the spinal cord and initiating the neurogenic inflammations that lead to peripheral sensitization. Normally, nociception leads to pain perception; yet, in some cases, like traumas, they might occur independently [17]. Pain perception could be altered if such mechanisms aren't functioning properly.

2. Degenerative Disc Disease

Lower back pain is the most common result of lumbar disc degeneration [18]. Lifestyle, mechanical loading, genetics, and nutrient transport all influence the activity and number of cells within the disc [18-20]. Because inter-vertebral discs are the body's largest avascular tissues, nutrition supplies to the disc are limited [21]. With increasing age, only a small number of the cells remained in the annulus which lose their capability of proliferating, playing a role in the disc degeneration [22, 23]. The degeneration of discs in the lumbar spine is more common, implying that mechanical strain is also a factor [24]. Aggrecan and collagen metabolism are affected by a combination of nutrition transport, genetics, lifestyle, and mechanical loads. The hydrophilicity and viscosity of nucleus pulposus are decreased as aggrecan has been broken up and its molecular number and weight decrease [25].

The nucleus pulpous hydrophilicity impacts its hydro-static pressure and, as a result, its nutrient supply by diffusion. The intervertebral height is reduced as the water content regarding

the extracellular matrix decreases, lowering the disc's resistance to axial load [25]. Nuclear materials can herniate through the annulus fibrosis because of the reduced resistance to axial load. Subsequent disc height loss leads to changing of the mechanics at facet joint and osteophytes formation which resulted in narrowing the neuro-foraminal and spinal canals [26].

3. Platelet-Rich Plasma

PRP can be defined as a small amount of plasma with high concentration of autologous platelets [27]. Platelets are a source of growth factors like transforming growth factor beta1 (TGF-β1), platelet-derived angiogenesis factor, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and others [28]. Factors that promote growth have an impact on wound healing as well as biological processes like neovascularization, chemotaxis, scar formation, and extracellular matrix synthesis [28]. PRP has a higher growth factor concentration, which is thought to assist in initiating of inflammatory response. As a result, PRP can be used to promote soft tissue healing, bone regeneration, and graft vascularization [29, 30].

Several studies have found that the optimal concentration of the platelets for the PRP to be therapeutic is (4-6) times larger compared to the whole blood (200,000 mm3) [30–32]. PRP might be injected or used topically, and it can be made in several ways [33]. leukocyte-rich PRP, Leukocyte-poor PRPs or Pure PRP (P-PRP), platelet-rich fibrin, platelet and leukocyte-rich fibrins are the four main categories of PRP types [33]. PRP was reported for the first time, as a treatment for patient with thrombocytopenia [34]. After that, it was used for treating bones in patients who have mandibular continuity when administered PRP and autograft bone resulted in considerable increases in the growth of the bones and graft density [35]. Since its initial use, PRP was studied in a different fields such as plastic surgery for facial rejuvenation, cardiac operation, orthopedics, dermatology, gynecology, and urology (Table 1) [34, 36, 37].

PRP has been most commonly used as a conservative therapeutic option in orthopedics, yet studies on its efficiency were conflicting [34, 38–42]. Using PRP in total knee arthroplasty

(TKA), ligament reconstruction, epicondylitis, osteoarthritis, hamstring injuries, rotator cuff repairs, high tibial osteotomy, and meniscal repair were examined in many researches [43, 44]. In a meta-analysis of 36 studies, PRP was compared to dry needling, local steroid injections, some conservative management approaches, and autologous whole blood in various orthopedic complaints [39]. They did not find a distinct advantage of using PRP in comparison with controls. In addition, a certain meta-analysis evaluating PRP utilization for osteoarthritis indicated improved pain levels after TKA but did not find any statistically significant clinical improvements [45]. A different meta-analysis, on the other hand, looked into using PRP in TKA and found that it improved ROM and pain intensity scores in comparison with placebo [41]. This indicates a variety of results when assessing PRP usefulness in treating musculoskeletal issues. Variability could be due to a lack in PRP preparation, method standardization, the frequency or amount of administered PRP and delivery approaches [44, 45].

Table 1. Latest Developments in the PRP

Authors	Subject	Interventions	Measured Outcomes	Results & conclusions
Tohidnezhed *et al*. [47]	In vitro model of the human inflammatory synoviocytes	Injection of the autologous PRP	IL-1β and TNFα cytokine expression and secretion	PRP decreases secretion and expression of the proinflamatory cytokine genes
Khlaf *et al*. [48].	Porcine inter-vertebral discs (IVD) that are denatured with the trypsin	Denatured discs have been treated by PRP and control fluids	Disc bulging fluid outflow, IVD stiffness, and glycosaminoglycan content	Injection of the PRP has resulted in the improvement of stiffness and fluid outflows in the denatured inter-vertebral discs; increased glycosamino-glycan contents
Yang *et al*. [49]	Osteoarthritis rat model: in vitro Chondrocytes as well as In vivo meniscal tear	Autologous injections of the PRP	Anabolic as well as catabolic expression of the genes, autophagy markers, and in vivo cartilage degenerations.	Injection of the PRP has resulted in increasing the anabolic gene expressions, decreasing the catabolic gene expressions, and ameliorated cartilage degenerations without having any impact on the autophagy markers
Khattab *et al*. [50].	Rat model, induced Osteoarthritis with the injection of the collagenase	Autologous PRP versus saline injections in the joints	Hind leg wt. distributions (pain surrogate), synovial inflammations, cartilage damages	Rats with the injections of PRP had shown more equal weight distributions; fewer anti-inflammatory cells in the joints that had been injected with saline

3.1 Basic Science of PRP

As the information regarding PRP's mechanism of action is expanded, so does number of possible applications. PRP and its constituents influence a wide range of pathways, according to basic science research. Whereas the exact mechanism of action is unknown, in vivo and in vitro investigations have revealed cellular and biochemical alterations related to mechanical structure and inflammation. By using human data and animal models, PRP injection research has revealed information about the chondroprotection, pain relief, and factors which influence therapy's efficiency. The treatments for inter-vertebral disc degeneration (IDD) had traditionally relied on pain relief rather than the reversal or stopping of underlying process. The growth factor and PRP therapy for the IDD were examined by Wang *et al*. [46] who discovered various cellular-level advantages in the inter-vertebral disc cells and tissues over 28 in vitro researches in a variety of tissue and cellular models, including human. PDGF, TGF-β1, VEGF, IGF, epidermal GF, and other active materials are released from platelet when activated; PDGF and TGF-β1, in particular, have been strongly linked to tissue repair and cellular remodeling. In the intervertebral disc's complex homeostasis, these factors have promoted matrix repair, cell proliferation, and survival of the nucleus pulposus.

Tohidenezhad *et al*. [47] investigate the role of growth factors in a model of the rheumatoid arthritis and reach to same conclusion. The impact of PRGF on inflammatory human synoviocytes, were measured with the use of real-time PCR and ELISA to detect the expression and presence of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β. IL-1β and TNFα gene secretion and expression were dramatically decreased in vitro after injections of the PRGF concentrate derived from the autologous, activated PRP. Whereas Tohidenezhad *etal*. and Wang et al. showed short-term advantages from the injections of the PGRF, which attributed mainly to growth factor and cytokine activities, long-term advantages have yet to be investigated, and the mechanisms of action are unknown. Furthermore, whereas the growth factors appear to be of high importance in anti-inflammatory and cellular repair process, autologous PRP therapies are less expensive, have longer half-life, and consists of GFs in the biological ratios in comparison with the synthetic or derived therapies of the GF [46, 47].

Khalaf *et al.* [48] in 2015, stated that PRP therapy can assist in the treatment of denatured intervertebral discs. PRP injections could restore fluid flow capability and disc stiffness even after they have been denatured with trypsin, according to their study on mechanical features of the inter-vertebral discs. Furthermore, glycosaminoglycan content in PRP-treated discs was significantly higher than in control discs, but didn't revert to pre-denaturation levels. According to this and abovementioned researches, PRP quiesces disease and inflammation processes as well as restore the structural integrity of the affected site.

At the cellular level, PRP regulates autophagy regardless of other protective effects. Yang *et al.* [49] found that both pure PRP (P-PRP) as well as leukocyte-rich PRP (L-PRP) reduced autophagy-related and osteoarthritis (OA)-related gene expression. PRP treatment increased anabolic gene expression while decreasing catabolic gene expressions in vitro model of osteoarthritis. Furthermore, in vivo experiments of OA rat models revealed decreased cartilage degeneration with no substantial changes in autophagy markers, as evaluated by light chain 3 expression. As factors of autophagy didn't show statistically significant difference in control vs. PRP-treated groups in in vivo as well as in vitro experiments, PRP-induced chondro-protection is separated from the mechanisms that regulate autophagy.

PRP treatment has been shown to be advantageous in the osteoarthritis treatment. In the case when mice were given collagenase injections to induce OA, the weight distribution in the hind legs enhanced dramatically after affected joint has been injected with the PRP therapy versus saline injections. Furthermore, at 21 days, microscopic examination of synovial membrane lining joint indicated significantly less inflammations [50]. Whereas such data doesn't indicate long-term effects of the injections of the PRP, it shows that repeated injections of the PRP in OA model reduce inflammation and pain.

Yang *et al.* [49] conducted a comprehensive literatures review to determine the usefulness of repeated administration, localization, and the type of PRP injection. Localization and outcomes were more specific and consistent when provided in a confined space (intervertebral disc and joint cavity) and in a solid form (PRP after activation).

Repeated administration resulted in a longer duration of effect in terms of pain relief, but this should be balanced against risks of procedural discomfort and infection [51].

3.2 PRP for Discogenic Pain

The injections of PRP appear to be a viable method to regenerate or rehabilitate disc tissue [52]. A few case studies, including those described by Lutz *et al*. [53] lately promoted PRP injections as fairly harmless treatment for patients who have the degenerative disc disease and failed to respond to existing treatments of lower back pains [53, 54].

Levi *et al*. [55] conducted a prospective experiment on group of 22 patients to determine safety and efficiency of PRP injections as treatments for discogenic lower back pains. Adults (12 female and 10 male) ≥ 18 years (median = 47.50 years) with image-based or clinical characteristics of discogenic back pains (median duration = 90months) and a visual analog score (VAS) ≥ 40.0mm made up the study population [56]. Prior to starting treatment, the Oswestry Disability Index (ODI) has been assessed as well [57]. Imaging or clinical cues have been employed instead of the discography for determining the vertebral level of injection site except in the case when provocative discography has been conducted earlier. Under fluoroscopy, 1.5mL PRP solution has been injected into target disc nucleus. A successful result has been specified as a 50% improvement in VAS and a 30% improvement in ODI, depending on the formerly-published definitions of minimally relevant changes in back pain following intervention [58, 59]. A total of 22/22 patients have been followed up at 1and 2-months after injection, and 19/22 patients have been followed up at six-months. At one and two months, 3/22 and 7/22 patients, respectively, had successful results. 9/19 had met criteria for a favorable result after six months. Throughout the course of this work, no negative impact of PRP injection therapy have been indicated to the researchers.

Levi *et al.* [55] prospective study presents limited evidences of the fact that the injection of the PRP might be safe and beneficial in some patients. The trial's results and findings are significantly confounded due to the lack of control groups, limited sample size, and lack of unified applied parameters of the diagnosis. Post-injection score enhancement delay for both disability as well as pain metrics from one to six months of the follow-up amongst a sub-set of participants was an interesting trend highlighted by the authors.

This study's findings may call for a re-evaluation or extension of a follow-up of post-PRP injection, along with more research into the underlying temporal features of PRP-mediated disc re-generation.

In a different prospective trail to assess efficacy of PRP injection as therapy for lower back pain, Akeda *et al*. [60] enrolled 14 patients who have chronic LBP, positive provocative discography, and MRI evidence of the degenerative lumbar discs. The scores of Roland-Morris Disability Questionnaire (RDQ) and VAS have been used in order to determine baseline LBP prior to treatment. For comparison to post-treatment images, Magnetic resonance and radiographic images of the lumbar spine have been saved as well. Provocative discography and MRI were used for confirming the presence of degenerative discs. Under fluoroscopy, 2mL of the PRP has been injected in the disc nuclei. The study population had demonstrated a significant reduction in the average LBP after 4 weeks, with 11/14 patients who have reported a higher than 50% improvement in RDQ. Such decrease in the sample low back pain has been maintained for a year. Surprisingly, there were no differences in sagittal MRI or radiograph properties between experimental and internal control vertebrae, as measured with the Pfirrmann disc degeneration grade or disc height index [61, 62]. After or during treatment, no negative impacts or safety concerns of the injection of PRP have been indicated.

At the same time, Akeda *et al*. [60] evaluated the efficiency of the injections of PRP for treating LBP. They showed sustained improvement in RDQ and VAS after 4 weeks of follow-up, indicating that PRP may be effective. Despite such findings, these studies have drawbacks such as a lack of a placebo-controlled group and limited size of the sample.

In a double-blind randomized controlled study, Tuakli-Wosornu *et al*. [63] have selected adults that had a chronic LBP history as well as an annular tear which confirmed by imaging. PRP was injected into degenerative discs in the experimental group, whereas fluorescent dye was put into the control group. Before therapy, scores on the Numeric Rating Scale (NRS), Functional Rating Index (FRI), and the 36-Item Short-Form Health Survey (SF36) had been collected to determine function/disability and baseline pain [64-66].

After 8 weeks of follow-up, NRS and FRI best pain scores were considerably lower in PRP group in comparison with the control group while the NASS Outcome Questionnaire revealed that PRP-treated patients have been substantially more satisfied with their therapy compared to the control individuals [67]. A fraction of treated patients showed significant improvements in pain and function over baseline, yet they were not put to comparison with the control group. Throughout therapy and follow-up, there were no safety issues.

PRP might be effective for treating LBP and other complications of degenerative vertebral discs, according to multiple, orthogonal metrics in this controlled, randomized trial. The authors tackle some of the confounding variables in Akeda *et a*l. [60] and Levi *et al*. [55] prospective trials. Longer periods of the follow-up, larger sample sizes, objective outcome metrics, and investigation of molecular mechanisms that are underlying disc re-generation should be considered in future trials to provide more reliable results. The results of researches evaluating the efficiency of PRP for discogenic pain treatment have been summarized in Table 2.

Table2. Preliminary trials that assess PRP injection safety and efficacy for treating discogenic lower back pain.

Author	Study Type	Populations	Interventions	Results	Conclusion
Levi *et al*. [55]	Prospective Trials	22 patients (12 females and 10 males) ≥ 18years old (median = 47.5 years) with the image-based or clinical characteristics of the discogenic back pains (median duration = 90months) and VAS ≥ 40mm.	1.5mL PRP has been injected at the levels of the lumbar spine, which has been determined by earlier discography, other imaging Modalities and/or clinical characteristics. ODI and VAS have been evaluated at 1, 2, and 6 months of the follow-up.	Efficient outcomes have been characterized as ≥ 30% improvement in the ODI and ≥ 50% improvement in VAS. 22/22 completed two months follow-up, 19/22 have completed six months follow-up. 7/22 and 9/19 obtained successful outcomes at two and six months.	After 6 months, PRP injections might provide the most effective. Due to the lack of unified criteria of diagnosis (provocation discography), the control group, as well as the short period of follow-up, the results might be confounded.
Akida *et al*. [60]	Prospective Trials	14 patients (6 females and 8 males) ≥ 18 years old. (mean of age = 33.80 years) with (a) > 3 months. Chronic LBPs (b) MRI evidence of the degenerative lumbar discs with the height of the disc > 50% and (c) positive provocative discography. Patients who have the neurological origins have been omitted.	2mL of the PRP had been injected at the symptomatic disc (or discs) confirmed with discography. LBP was assessed through VAS and RDQ and evaluated at 4, 8, 16, 24, 32, 40, and 48weeks after the treatments. %△ DHI in the vertebrae of the lumbar was evaluated via radiograph. Changes in Pfirmann disc de-generation grade was assessed via sagittal MRI.	14/14 had followed up 0-6 months. 10/14 had followed up for ten months and 9/14 had completed the follow-up for 12 months. 10/14 had found more than 50% improvement in the score of VAS at 4 weeks and 11/14 had reported more than 50% improvement in the RDQ. Significant reduction in the average values of the RDQ and VAS has been continued for 12 months. No changes in the metrics of the radiograph or MRI were notified in the control versus the experimental vertebrae	.PRP injection is a potentially safe and effective treatment for LBP. For supporting the utilization of the PRP for pain management and disc regeneration, mechanistic studies and randomized, placebo-controlled trials are required.
Tuakli-Wosornu *et al*. [63]	Prospective, controlled, randomized, trial	47 patients (31 females and16 males) ≥ 18 years. Mean age = 42.30 years) with (a) LBP > 6 months, (b) height of the disk > 50% with a protrusion of less than 5mm, and (c) annular fissures had been confirmed by the positive provocative discography; had failed conservative management.	The participants have been randomly classified into the control group and the PRP treatment group. FRI, NRS, and SF36 scores have been evaluated at the baseline. (1–2) mL of the PRP and contrast injected. The scores of NRS, FRI, SF36, and NASS have been compared after the treatments with the PRP. Follow-up surveys have been administered at one, four, and eight-week periods. At six and 12 months after the treatment, the PRP group function and pain scores have been compared with the baseline.	The PRP group FRl and NRS optimal pain scores have been improved significantly at 8 weeks in comparison with the controls. In comparison with the controls, the PRP group members have been significantly more satisfied with the treatments (via NASS). At 12 months follow-up, the group of the PRP had shown significant and sustained improvement in the values of the FRI, NRS worst pain, and SF36 metrics in comparison with the baseline. No concerns about safety have been reported throughout the treatment or at the time of follow-up.	The first randomized clinical study investigated the effectiveness and safety of PRP as an LBP treatment. For future trials, more uniform diagnostic outcomes and standards metrics should be provided. Data power is limited by the small size of the sample and the eight weeks of control. There is no clear trend in pain or function metrics

platelet-rich plasma (PRP), low back pain LBP, Roland-Morris disability questionnaire (RDQ,) visual analog scale (VAS), Oswestry Disability Index (ODI), Functional Rating Index (FRI), disc height index (DHI), 36-Item Short-Form Health Survey (SF-36), Numeric Rating Scale (NRS), North American Spine Society Outcome Questionnaire (NASS)

3.3 PRP for the Sacro-iliac Joint (SIJ) Pains

The conventional interventions for the SIJ pains play therapeutic as well as diagnostic roles. Simopoulos *et al*. [68] graded evidence for many therapeutic and diagnostic approaches in a systematic review that has been published in 2015 and found mediocre evidence for some of the most regularly utilized procedures. At the same time, PRP injections for SIJ pain seem of high potential in the long- and short-term, even though the majority of trials have a limited sample size [69, 70]. SIJ pain is difficult to diagnose because there are so many different reasons for persistent lower back pain. MRIs, X-rays, and procedures like Patrick's test, sacral thrust, and Gaenslen's test are all common diagnostic tests [69]. Whereas such approaches are useful for diagnosing pain caused by SIJ instability or dysfunction, therapies that improve mobility and pain are also utilized for diagnostic purposes. Simopolos *et al*. [68] investigated the data from 11 kinds of research, to see if evidence for each one of the interventions was reliable in terms of diagnostic success. The researchers used USPSTF standards to rate evidence depending on both quantitative and qualitative metrics. They concentrated on clinically important results, which often needed a greater improvement in mobility and pain compared to the threshold utilized in a wide range of the previous research; for the diagnostic research, outcomes included $\geq 50\%$ or $\geq 80\%$ decrement in pain, as well as the capability for performing the previously-painful motions. Even though the diagnostic data has been quite heterogeneous, preventing real meta-analyses, the evidence was nonetheless worthy of being rated with the use of scoring systems previously discussed. In the case when a pain reduction of at least 70% was employed as the threshold for diagnosis, the evidence for the controlled diagnostic blocks has been rated as level II. With level II - III evidence in comparison to the level III evidence, dual blocks had better evidence compared to the single blocks. Only 18% of the patients that reported less-than-threshold relief on the 1st block were positive for the 2nd block, indicating that such diagnostic blocks had minimal rates of the false-negative results [68].

In the overview of therapeutic interventions, data has been extremely heterogeneous for formal meta-analyses. Nevertheless, evidence from 6 randomized controlled trials (RCT) and 8 observational studies has been sufficient to evaluate evidence for commonly conducted intervention types.

Just level IV evidence exists for intra-articular and periarticular injections. Cooled radio-frequency (RF) neurotomy presented better performance than conventional radio-frequency neurotomy when leveling II to III evidence, in comparison with levels III to IV evidence respectively. Furthermore, a lot of such studies didn't investigate the outcomes in the previous three months, and the ones that did often observed a significant decrease in intervention efficiency after a year [68].

Singla *et al*. [69] in 2017, published RCT results comparing the steroid injections to the injections of PRP for the SIJ pains, and the outcomes were positive in the short term. A total of 40 patients who had at least three provocative tests and have been identified with the pathology of the SIJ on MRI, X-ray, or nuclear scans were randomized into one of two groups: PRP or steroid. The latter had an intra-articular injection of methylprednisolone guided by ultrasound, whereas the PRP group received an autologous, filtered (leukocyte-free) PRP injection guided by ultrasound. All of the patients have been between the ages of 18 and 65, with an ASA grade I or II, and none had been lost to follow-up. The pain was the measured outcome by using Modified Oswestry Disability Questionnaire (MODQ) scores, visual analog scores (VAS), short-form health survey (SF12), and short-term and immediate consequences have been also assessed. Patients were assessed by such metrics at 2, 4, and 6 weeks, as well as at 3 months. There have been no significant differences in any metrics between PRP and steroid groups from pre-injection to 4 weeks after the injection, even though the two groups indicated improvements in MODQ scores, VAS, and SF12 scores. The MODQ, VAS, and both mental as well as physical health component scores of SF12 improved significantly more in the PRP group at 6 weeks and 3 months. The most significant difference was at three months, when 25% of patients in the steroid group had recorded they were pain-free, in comparison with 90% of the patients in the PRP group. When it came to the complications, the PRP group had a higher rate of post-injection stiffness and pain. These effects were only present for a short time after the injection and were all described as mild [69]. This research was promising, yet it had certain flaws, the most notable one was the small sample size. Furthermore, this work's exclusion criteria included a history of radicular pain, intervertebral disc disease, and excessive use of narcotics [69].

A significant decrease in opioid use could be a notable consequence of SIJ pain management, particularly given the present opioid epidemic worldwide. These patients and others who had additional possible back pain sources, like IVD, might give ambiguity to the results of this research; such populations must be taken into account in the future for determining possible effects on patients who have established severe, opioid dependence and refractory LBP.

In 2017, a case study that included 4 female patients having chronic SIJ pain revealed very good effects of PRP injection. Those females ranged in age from 45 to 67 years. with SIJ instability 2^{nd}–3^{rd} grades, and pain that was resistant to various treatments such as tramadol, non-steroidal anti-inflammatory drugs (NSAIDs), prolotherapy, opioids, and local injections. Under ultrasound guidance, each one of the patients had two autologous PRP injection sessions at Hackett's sites B, A, and C. The numerical rating scale (NRS), short-form McGill pain questionnaire (SFM), and Oswestry LBP and disability index were employed by Ko et al., which were comparable to those utilized in Singla et al RCT. The patients have been re-examined at 1- and 4-years following therapy after acquiring baseline data and executing the intervention. At one year, patients reported improvements in NRS, SFM, and Oswestry index of 88%, 93%, and 75%, respectively. At four years, pain metrics have been significantly improved, albeit less so compared to at one year, whereas disability improvement remained consistent across 1st and 4^{th} years. Furthermore, all 4 patients have been capable of returning to their pre-injury activity levels [70]. Injections of the PRP for SIJ pain remain widely used, despite the lack of evidence for their efficacy outside of small RCT and case reports so more data is required for a better assessment of PRP injections. Despite the lack of evidence for existing therapeutic and diagnostic approaches, innovative therapy for SIJ pain and lower back pain must be encouraged. More data on PRP injections will be accessible over time, and the few studies that are already available suggest promising long- and short-term efficacy in improving mobility and pain [69, 70].

3.4 PRP for the Facet Arthropathy

The facet joint of the spine is important for the mobility of the spine and carries a significant mechanical load. FJS is one of the common causes of LBP that is caused by joint degeneration leading to osteoarthritis [71]. Radiating lumbar discomfort, morning stiffness, and pain with the usage of joint and spine extension are common symptoms of facet joint osteoarthritis. The diagnosis is clinical, and it must rule out other pathologies like rheumatoid arthritis [72]. A modest number of potential studies lately suggested that PRP injection might be beneficial in treating pain or functional deterioration resulting from FJS.

Wu *et al*. [73] in 2016, evaluated the effectiveness of PRP injection in treating back pains with the FJS clinical sign and imaging that indicated degenerative variations in the facet joints. The PRP has been administered into the facet joint via intra-articular injection under fluoroscopy. At three-month of follow-ups, the VAS had continued to decline. Mean ODI and RDQ (at 3 months follow up) have also been significantly decreased in post-treatment patients in comparison with baseline. McNabb's status plateaued at "excellent" or "good" at the 1-month follow-up period in 15/19 patients, in comparison with 9/19 before therapy. Throughout the study, no negative impacts of PRP injection were indicated. According to the author of this prospective study, PRP injection might have therapeutic advantages in FJS treatment. For validating the trends in pain/disability reduction reported through this investigation, controlled, larger, randomized trials with more rigorous criteria of the selection would surely be required. Furthermore, longer follow-up periods could help in detecting symptom rebound or persistent therapy response.

Wu *et al*. [74] in 2017, Evaluate the efficiency of injected PRP in comparison with the injected anesthetic/corticosteroid solution in a later controlled, randomized prospective research. This research included patients who have back pains, clinical symptoms of FJS, and imaging that showed degenerative effects. Following 1 week, both corticosteroid and PRP showed a considerable reduction in VAS compared to baseline, which lasted for six months.

Corticosteroid's performance surpassed PRP at one week and one month, however, PRP improved more at 3 and 6 months. There were no problems due to treatments. Wu *et al*. [74] present strong preliminary data in favor of PRP as a long-term treatment option for FJS. Whereas anesthetic/corticosteroid injections might offer more immediate relief from the FJS, the PRP injection exhibited consistent improvements in function, pain, and satisfaction evaluations metrics, which might last beyond the 6-month follow-up period. Despite the larger sample size and addition of a randomized control which provides a significant improvement over Wu *et al.* [73] design, the outcomes are nevertheless confounded by the lack of rigid inclusion criteria and negative control. Those confounders most possibly resulted from a small recruiting pool and may be addressed in future multi-institutional trials. Table 3 summarizes the findings of research evaluating the efficacy of PRP for treating facet joint arthropathy-related pain.

Table3. Preliminary studies evaluating the safety and efficacy of the PRP injections for treating facet joint arthropathy

Author	Study Type	Populations	Interventions	Results	Conclusions
Wu *et al*. [73]	Prospective trials	19 patients (11 females and 8 males) ≥ 18 years (mean age of 52.530) with back pains and (a) clinical FJS symptoms or (b) positive imaging. Included no patients who have neurological insufficiencies or Radiculopathy.	Intra-articular injections of 0.5mL PRP in the facet joint. VAS mean (at rest, flexion), ODI, RDQ, and Mac-Nab criteria had been investigated before the treatment, right after the treatments, and one week, one, two, and three months after the treatment.	The average VAS (rest/flexion) has been reduced from base-line (7.05/8.42) to three months follow-ups (2.63/2.95). The average value of the RDQ has been significantly ($p < 0.05$) decreased in comparison with the baseline. ODI has been significantly (> 10%) decreased. McNabb's status was "good" or "excellent" in 15/19 patients in comparison with 9/19 before the treatments.	Injections of PRP could result in providing relief of the LBP resulting from the FJS within one week - to three months of treatment. The research has been confounded by limited sample size, subjective metrics of the pain, as well as a lack of the placebo-controls.
Wu *et al*. [74]	Controlled, Randomized prospective trial	46 patients (27 females and 19 males) ≥ 18 years, mean age of 52 years with the back pains and (a) clinical FJS symptoms (b) Imaging that is positive for the degenerative changes. Included no patients who had the neurological insufficiencies or radiculopathy.	Classified to the PRP (A) group and anesthetic (B) group. 0.5mL PRP or anesthetic to facet joints. VAS (at rest, flexion), ODI, RDQ, and criteria of MacNab had been surveyed before the treatments, right after the treatment, and one week, 1, 2, and 3 months after the treatment.	A and B groups had shown sustained and significantly reduced VAS after one week. Group B's performance had significantly surpassed A at one week and one month of the follow-up. The improvement of Group A in the VAS has been significantly higher at three months follow-ups. The VAS trend has been mirrored with the ODI and RDQ. MacNab satisfaction of B has been at the maximum at 80% at one month, however, it dropped to 50% at six months. MacNab satisfaction of Group A increased at a steady rate to 80% at six months follow-ups. There have not been any complications from the treatment	In all of the metrics (i.e. pain, satisfaction, and function), Group B's performance has been higher than A's in the short-run (less than 3 months). Group A had shown better outcomes that increase at a steady rate with the progression of follow-up. Whereas the anesthetic/corticosteroid injections could provide a higher level of relief from the FJS at first, the injections with PRP could serve better long-term therapeutic effects. This research has been confounded by the lack of the negative controls.

4. Conclusion

Despite the significant advance in the last few decades. Low back pains are still very common and difficult to treat. Patients who have chronic LBP caused by degenerative diseases of the lower back and spine might find platelet-rich plasma to be a safe and efficient treatment option. PRP has been shown effective in treating sacroiliac joint-associated pains, degenerative disc disease, and facet joint arthropathy in a recent few studies. Yet, larger clinical trials are needed in the future to better analyze the treatment's safety and efficacy.

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