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Title: Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review

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Introduction

Regenerative injection-based therapy has established itself as a therapeutic option for the management of a variety of painful musculoskeletal conditions. The aim of this work is to review the current literature regarding regenerative injection therapy for axial/radicular spine pain.

Methods

A comprehensive literature review was conducted on the use of regenerative medicine for axial/radicular spine pain. Eligible papers analyzed therapeutic injection effects of platelet-rich plasma (PRP), prolotherapy, or mesenchymal signaling cells (MSCs) via intradiscal, facet, epidural, or sacroiliac joint delivery.

Results

Intradiscal: PRP, level I/IV studies supporting its use. Prolotherapy, level III-IV studies supporting its use. MSCs, level I/IV studies supporting its use with the exception of one level IV study that found no significant improvement at 12 months.

Facets: PRP, level I/IV studies supporting its use. Prolotherapy, level IV studies supporting its use, though the one level I study did not demonstrate any statistical significance supporting its use.

Epidural: PRP, level I/IV studies supporting its use. Prolotherapy, level IV studies supporting its use, though the one level I study did not demonstrate statistical significance beyond 48 hours.

Sacroiliac joint: PRP, level I/IV studies supporting its use. Prolotherapy, level I/III studies supporting its use.

Conclusions

Currently, there are level I studies to support the use of PRP and MSCs for discogenic pain, facet PRP, epidural autologous conditioned serum and prolotherapy, as well as PRP and prolotherapy for sacroiliac joint pain. Facet prolotherapy has one level I study showing no significant benefit. Notably, no intervention has multiple published level I studies.

1.1 INTRODUCTION

Over the past decade a proliferation of treatment options under the titles of orthobiologics, regenerative medicine and interventional orthopedics have become available. Due to the specific nature of these therapies, the wide array of treatment options and the lack of insurance coverage, it remains difficult to report epidemiological data accurately. For pain of spinal origin, they are becoming more routinely available and include platelet-rich plasma, bone marrow concentrate,

prolotherapy, mesenchymal signaling cells and other biologic signaling factors. Their increasing use in the treatment of spinal pain is being driven by two main factors. Through word of mouth and anecdotal stories from peers, certain patients may be skeptical of conventional treatment's ability to provide durable, long-term relief. The second factor is the search for non-surgical, holistic, and "natural" remedies to promote self-healing. Historically, there has been a paucity of high-quality peer-reviewed evidence for orthobiologic use. This, however, is changing as orthobiologic treatments come to the forefront with the emergence of well-designed trials published in recent years.

Pain originating from the spine, especially pain poorly responsive to "standard of care" treatment modalities, has long posed challenges for healthcare providers and the greater healthcare system at large. Axial spine pain has been reported at least since the dawn of modern history, having even been described by Hippocrates in his book "On the Articulations".[1] The problem remains substantial as "back problems" are the leading cause of years lived with disability and the third most prevalent reason for ambulatory office visits.[2,3]

The high incidence of back pain places an enormous economic burden on the healthcare system. Dieleman *et al.* found health care spending on just low back and neck pain increased 2nd most as compared to 155 other medical conditions between 1996 and 2013.[4] The average adjusted medical cost per year is $3,600 greater for those with low back pain and increasing resources are being allocated to its treatment and diagnosis, with estimated expenditures increasing 65% from 1997 to 2005.[5] Unfortunately, despite expenditures increasing 8% per year, low back pain chronicity and disability continue to rise. Clearly, back pain is a growing financial healthcare burden.

In light of the growing cost, incidence, and prevalence of people experiencing chronic back pain, alternative and improved treatment options have been a major point of emphasis.[6] One major treatment, opioid analgesics, has been proven to be ineffective for management of these types of injuries, and has led to a healthcare crisis in its own right. According to the Centers for Disease Control and Prevention (CDC), use of prescription opioids has quadrupled since 1999; however, the amount of self-reported pain in America has remained unchanged.[7] The CDC also reported that opioids accounted for over 47,000 deaths in 2017.[8] Additionally, given the current opioid misuse epidemic, the CDC recommends significant caution in opioid prescribing for chronic non-cancerous pain management and offers extensive guidelines regarding best-practice when there is a decision to prescribe.[9]

Another common treatment modality for many musculoskeletal conditions is corticosteroid injections. There are limitations to this treatment though with regards to frequency, duration of effect, as well as growing literature demonstrating the potential teno-toxic and chrondro-toxic properties associated with these injections.[10] In general, interventional pain procedures have seen an enormous increase in utilization over recent years, from 2000 to 2011 a 228% utilization increase was shown, and Medicare paid over two billion dollars in 2006 alone for them.[11] The largest increase was for facet interventions at 386% and sacroiliac joint blocks at 310%, but other techniques such as epidurals (186%) and percutaneous disc procedures (28%) also saw a rise.[11]

In addition to these more routine treatments, there exists a multitude of other treatment options for spine-related pain. Orthobiologic therapy is an alternative treatment option in the multi-modal management of pain.[12] As new treatment modalities emerge, it is a medical and ethical necessity to continually review and assess the available literature for the

effectiveness of available therapies. This narrative review aims to assess the currently available literature as it relates to the use of orthobiologics for the treatment of axial spine and radicular pain disorders. For the purpose of this review, these disorders included all studies addressing zygapophyseal joint, discogenic, and radicular pain ranging from the cervical to lumbar spine as well as sacroiliac joint pain.

1.2 EPIDEMIOLOGY

Pain originating from the spine is incredibly common, with an annual point prevalence of 13% for chronic low back pain and 4.9% for neck pain.[13,14] The overall prevalence is likely higher than reported as this pain is best documented in high-income populations with limited data from their middle and lower income counterparts.[15] The most common pain generators in the lumbar spine are the intervertebral disc and zygapophyseal, or facet, joints. Up to 50% of low back pain in patients treated at specialized pain or orthopedic clinics is alleged to be of discogenic origin while facet-mediated pain may account for another 33%.[16,17] In the cervical spine, facet-mediated pain predominates and has been estimated to account for 40-60% of non-neuropathic neck pain.[18] Age plays a significant factor as low back pain is rare in children before they reach school age and rises in prevalence until 18 when it matches adult rates.[19] It should be noted that in addition to nociceptive spine pain exists radicular pain. Radicular pain is pain radiating along a nerve root without neurologic involvement. This differs from the typical nociceptive pain in that the axons are stimulated from the perinevrium and not the peripheral nerve terminals.[20] Colloquially this is often called neuropathic pain. Prevalence of neuropathic low back pain has been reported at approximately 5%.[21]

2. METHODS

A comprehensive literature review was conducted on the use of regenerative medicine for axial spine and radicular pain. The following electronic databases were used for the search: PubMed, Google Scholar, and The Cochrane Library.

Searches were performed for each orthobiologic agent: platelet rich plasma (PRP), prolotherapy, and mesenchymal signaling cells (MSCs). PRP search terms were: “platelet rich plasma” OR “PRP” AND “discogenic” OR “disc” OR “facet” OR “epidural” OR “radicular” OR “sacroiliac”. Prolotherapy search terms were: “prolotherapy” AND “discogenic” OR “disc” OR “facet” OR “epidural” OR “radicular” OR “sacroiliac”. MSC search terms were: “bone marrow aspirate concentrate” OR “BMAC” OR “adipocyte signaling cell” OR “ASC” AND “discogenic” OR “disc” OR “facet” OR “epidural” OR “radicular” OR “sacroiliac”.

Eligible papers were written in English and analyzed therapeutic injection effects of PRP, prolotherapy, or MSCs via intradiscal, facet, epidural, or sacroiliac joint delivery on human patients diagnosed with spine-related pain. PRP, prolotherapy, and MSCs were the three orthobiologic agents chosen to include within this review because they are the most common agents used for regenerative injection-based therapy in musculoskeletal medicine and are the most well-studied.[22] Exclusion criteria were case reports and studies in which spine-related pain was not the principal diagnosis. Three authors (D.R, J.T.M, B.M) screened the titles and abstracts to identify potentially eligible studies. If an article was not immediately excludible from its abstract, a full text-review was performed. Out of the initial 239 articles, 35 met the

inclusion criteria and were included in this review. The primary outcomes for most studies were pain or disability. Details regarding the study search are included in Figure 1.

3. ORTHOBIOLOGICS & THE LITERATURE

3.1 Orthobiologics Description

The American Academy of Orthopedic Surgery describes orthobiologics as "the use of biological substances to help musculoskeletal injuries heal quicker. They are used to improve the healing of fractured bones and injured muscles, tendons and ligaments and are derived from substances that are naturally found in the body. When they are used in concentrations many times the normal, they can potentially help speed up the healing processes".[23] Commonly, these injections are composed of cells, scaffolding, and growth factors. The most common orthobiologics administered for the treatment of musculoskeletal pain are platelet rich plasma (PRP), prolotherapy, and mesenchymal signaling cells (MSCs). MSCs primarily consist of bone marrow aspirate concentrate (BMAC) and adipose signaling cells (ASCs). In this section, we review their proposed mechanisms of action and thus why they are emerging as promising treatment options for pain.

Platelet Rich Plasma

PRP consists of an autologous concentrate of platelets made from centrifugation of whole blood to increase platelet concentration with the removal of other cellular components. For efficacy, the platelet concentration must be higher than baseline. The proposed mechanism for PRP as a therapeutic is that PRP initiates the body's own repair processes, modulates inflammation, delivers growth factors, and attracts and activates mesenchymal stem cells which promote a healing environment and reduce pain.[24] In vitro studies have shown PRP to induce downregulation of the crucial inflammatory molecules IL-6 and IL-8, which can help attenuate hyperalgesia.[25]

Preparation standardization has been recommended to better guide clinical application, the PLRA classification system described by Mautner *et al.* provides the most current comprehensive classification system.[26] This system includes platelet count, leukocyte content, red blood cell content, and activation status. PRP injections can be performed at the point of care and with a low rate of adverse events.

Prolotherapy

Prolotherapy involves an injection of a solution not containing biologic material with the goal of repairing connective tissue and ameliorating pain. Most commonly, hypertonic dextrose is used, but phenol and sodium morrhuate have been described as well. These three proliferants represent the different classes of prolotherapy: osmotic agents, irritants, and chemotactic agents, respectively. Irritants damage cell membranes and chemotactic agents are thought to directly induce the inflammatory cascade. Osmotic agents cause local tissue irritation, leading to recruitment of inflammatory cells which may trigger a healing cascade.[27] Dextrose is the most well studied and viewed as the ideal proliferant because of its water solubility and ability for safe injection into multiple areas.[28]

Mesenchymal Signaling Cells

MSCs are cells with the perceived capability to proliferate and differentiate into cells that regenerate tissue functionality following injury.[27] They are perivascular in origin and can be isolated from any vascularized tissue.[29] Initially described to be present in bone marrow by Dr. Alexander Friedenstein, these regenerative cells have now also been shown to be present in peripheral blood, skeletal muscle, and adipose tissue. *In Vitro* studies have shown these cells to express growth factors such as transforming growth factor beta and vascular endothelial growth factor, which are known to stimulate local tissue repair.[30] Additionally, they suppress the proliferation of inflammatory T-cells and inhibit monocyte maturation creating both immunomodulatory and anti-inflammatory effects.[30,31] Their ability to decrease inflammation and promote tissue repair has sparked an increase in their usage for the treatment of musculoskeletal pain. Most commonly, bone marrow aspirate and fat transfer techniques are used in regenerative medicine.

Bone Marrow Aspirate Concentrate

BMAC is the term used to describe the MSCs and marrow elements obtained from bone marrow aspiration. The posterior iliac crest is most commonly used as it has been shown provide the highest concentration of MSCs.[32] The aspirate must undergo density gradient centrifugation to isolate progenitor cells as they account for a small population of the cells within bone marrow (0.001% to 0.01%).[33] BMAC has been shown to serve as a source for growth factors such as PDGF, TGF-B and BMP-2 that have anabolic and anti-inflammatory effects.[34] Bone-marrow derived platelets included in BMAC differs from those of peripheral blood used in PRP and have been shown to provide additional growth factors and potentially aid chondrogenesis.[35,36]

Adipose-Derived Signaling Cells

ADSCs are MSCs that have been isolated from homogenized adipose tissue through lipo-aspiration. Adipose provides an excellent medium for MSC harvest secondary to its abundant vasculature. The procurement procedure consists of a minimally invasive harvest with higher cell concentration per unit volume and less susceptibility to culture expansion senescence compared to BMAC. Numerous mechanisms have been proposed to explain how ADSCs may support repair and help regenerate tissues. As described previously, secretion of cytokines and growth factors through a paracrine mechanism likely play a large role. Pagani *et al.* demonstrated *in vitro* that ADSCs had higher matrix composition and gene expression compared to BMAC that may improve chondrogenic potential in an inflammatory environment.[37] Release of free radical scavengers and antioxidants elicited from ADSCs may promote cell survival and help remove toxic substances, which could help mediate the inflammatory response.[38]

3.2 Orthobiologic Treatments for Axial Spine and Radicular Pain: Current Literature

Here we provide the available literature on regenerative medicine therapeutics for treating spine-related pain categorized via injection delivery location: intradiscal, facet joint, epidural, and sacroiliac joint. Levels of evidence for each study

were determined by the criteria of the American Association of Physical Medicine & Rehabilitation, an adaptation of those proposed by *The Journal of Bone and Joint Surgery*.[39]

- Level I – Randomized controlled trials or systemic review of level I randomized controlled trials.
- Level II – Prospective cohort studies, poor-quality randomized controlled trials, systemic reviews of level II studies or non-homogenous level I studies
- Level III – Case-control studies, retrospective cohort studies, systemic reviews of level III studies
- Level IV – Case series
- Level V – Expert opinion

Discogenic

Table 1a-c: Discogenic Orthobiologic Studies

PRP

Table 1a summarizes the characteristics and results of the currently available studies regarding intradiscal PRP. There is only one level I study and multiple level IV studies on the effects of intradiscal PRP. Through a double-blind randomized control trial, Tuakli-Wosornu and colleagues demonstrated intradiscal PRP versus an Omnipaque 180 contrast control to provide significant improvement at 8 weeks regarding pain and function. Results were sustained at 1 year for the PRP group, but notably comparative outcomes versus control were not evaluated after 8 weeks.[40] Four additional studies analyzed PRP and one analyzed autologous leukocyte-reduced PRP outcomes.

Regarding prospective trials, the results were positive for PRP with pain outcomes improving in the majority of PRP treated patients.[41,42] Notably, the Comella et al. study used a combination of stromal vascular fraction (SVF) and PRP for their injectate; SVF is a combination of adipose-derived signaling cells and growth factors. The remaining prospective PRP study found 47% of patients had greater than 50% improvement in Visual Analog Scale (VAS) and 30% decrease in Oswestry Disability Index (ODI) at 6 months.[43]

Kirchner *et al.* performed a retrospective observational study utilizing one facet joint, one intervertebral disc, and one epidural injection of autologous leukocyte-reduced PRP in 86 patients with chronic low back pain and found significant improvements in VAS scores, with 91% reporting an "excellent" score.[44] Of note, all three targets were injected in the same visit. Additionally, Navani et al. performed a case series in which patients received either intradiscal PRP or BMAC-MSCs. This study found 93% of patients achieved greater than 50% reduction in verbal pain scale (VPS) at 18 months. It is noteworthy though that there was no distinction regarding which or how many patients received PRP versus BMAC-MSC.[45]

Prolotherapy

Table 1b summarizes the characteristics and results of the currently available studies regarding intradiscal prolotherapy. There are two published studies on the use of prolotherapy for discogenic spine pain. Both studies reported positive results but are limited by low level studies (III/IV). Additionally, the efficacy of intradiscal prolotherapy is difficult to ascertain in

the case of Derby et al. because the injectate was a mixture of hypertonic dextrose, glucosamine/chondroitin, and dimethylsulfoxide. Having said that, this study demonstrated intradiscal prolotherapy(+) provided significant pain improvement compared to a intradiscal electrothermal treatment group.[46] In the other intradiscal prolotherapy study, a prospective series on 76 patients, slightly less than half had sustained improvement in numeric pain scores at 18 months.[47]

MSCs

Table 1c summarizes the characteristics and results of the currently available studies regarding intradiscal MSCs. There is one level I study available, where VAS, ODI, and lumbar disc degeneration assessed using the Pfirrman grading system significantly improved in a randomized controlled trial of intradiscal BMAC compared to sham (1% mepivacaine).[48] The remaining literature consists of prospective or pilot studies. Four studies analyzed the effects of intradiscal MSCs. Three showed improvement in measured pain and disability scores with follow-up periods of at least one year.[49-51] The lone negative study showed no improvement in numeric pain scores at 1 year after intradiscal BMAC-MSCs followed by 2-week course of hyperbaric oxygen therapy.[52]

Three additional studies were included in this review, yet they utilized different injectates, which needs to be taken into account when interpreting their results. Kumar et al. used a combination of ASCs and hyaluronic acid derivatives for their injectate.[53] This study found 60% of participants achieved 50% or greater reduction of pain. Coric et al. used cell-based NuQu allogenic juvenile chondrocyte cells for their injectate.[54] The decision was made to include this study because the intervertebral disc is a fibro-cartilaginous structure, and the injectate used was a precursor to this. Mochida et al. used a combination of nucleus pulposus chondrocytes co-cultured with BMAC-MSCs for their injectate.[55] Each of these studies found significant improvement in pain scores after treatment.[54,55]

Facet

Table 2a-b: Facet Orthobiologic Studies

PRP

Table 2a summarizes the characteristics and results of the currently available studies regarding facet joint PRP. One level I study is available for treating facet-mediated pain with PRP. Wu et al. found both intraarticular facet injections with PRP versus corticosteroid/local anesthetic both resulted in significant improvement in VAS, RMQ, and ODI at one month while only the PRP group had sustained improvement through six months.[56] There are three additional level IV studies regarding the use of PRP for facet-mediate pain. Wu and colleagues previously published a prospective series that found significant improvement in VAS at rest and with flexion, RMQ, and ODI at three months.[57] Additionally, level IV studies via a retrospective observational study and case series both showed decreases in VAS.[44,58] It is noteworthy, the Kirchner et al. study discussed above (Discogenic PRP) is again included here. See above for details.[44] It is also worth noting that Aufiero et al. injected both the intraarticular facet joints as well as surrounding ligaments.[58] This should be considered when interpreting those results.

Prolotherapy

Table 2b summarizes the characteristics and results of the currently available studies regarding facet joint prolotherapy. One level I study exists for the treatment of facet-mediated pain using prolotherapy. Dechow et al. found no significant difference in pain outcomes (SF-MPQ) at 6 months between the treatment group and the normal saline with 1% lignocaine control group. Notably the injectate used for this study was a mixture of hypertonic dextrose, glycerine, phenol, and lignocaine. Additionally, not only the facet joints were injected, but several locations along the iliolumbar and posterior SI ligaments. The results of this study should be interpreted with these caveats in mind.[59] Additionally, there are three published studies by Hooper and colleagues, with one being prospective and two retrospectives. The prospective study found intra-articular facet prolotherapy with 20% dextrose provided significant improvement on multiple analyzed disability scales over a 12 month period.[60] The vast majority of patients reported a reduction in their level of pain, improvement in activities of daily living and ability to work in a retrospective case series on 177 patients with chronic spinal pain treated with 20% dextrose prolotherapy facet injections.[61] The final study had a much lower sample size of 15 patients with chronic cervical whiplash, and demonstrated a significant reduction in neck disability index scores.[62] All three studies by Hooper and colleagues involved facet intervention in the cervical spine for at least a portion of their cohort.

MSCs

No studies to date have been published on the use of MSCs administered to the facet joints.

Epidural

Table 3a-b: Epidural Orthobiologic Studies

PRP

Table 3a summarizes the characteristics and results of the currently available studies regarding epidural PRP. The only level I epidural study does not actually involve PRP, but an analog called autologous conditioned serum (ACS) which is similarly obtained through phlebotomy but instead functions as an anti-inflammatory agent through interleukin antagonism promotion. Pain reduction in both the ACS and steroid control groups was observed, with more sustained pain relief in the ACS group.[63] Two other prospective studies currently exist, with a registry of 470 patients treated with platelet lysate (PL) by Centeno *et al.* being the largest and observing significant numeric pain score changes through all time points compared to baseline.[64] While there were no serious adverse events reported, 6.3% reported mild adverse events related to the treatment. PL is slightly different than PRP, in that PL is created by lysing platelets and removing the cell debris. This resultant product is rich in growth-factors (similar to PRP) but devoid of other platelet material. This should be taken into account when interpreting results. Correa et al. found epidural autologous leukocyte-reduced PRP significantly improved VAS and MACNAB for 250 patients throughout two years of follow-up in the other prospective study.[65]

Retrospective analyses comprise the remaining three publications. Two showed VAS improvement after epidural PRP administration that was sustained for 3 months in one and 6 months in the other.[44,66] It is noteworthy, the Kirchner et al. study discussed above (Discogenic PRP) is again included here. See above for details.[44] The study by Bhatia *et al.* also

found that all participants were able to maintain daily activities without the use of pain medications.[66] Additionally, Kumar showed VAS was improved in 20 patients treated with epidural ACS.[67]

Prolotherapy

Table 3b summarizes the characteristics and results of the currently available studies regarding epidural prolotherapy. There is one level I study that demonstrated epidural prolotherapy to be efficacious in relieving pain up to 48 hours but the results did not differ from placebo at 2 weeks.[68] That same group assessed repeat injections as needed over the course of one year in the previous study cohort and found clinically significant improvement in NRS and ODI outcome measures.[69] These studies highlight the issues with single injection prolotherapy and the need to assess the effect of serial prolotherapy epidurals for long-term pain relief.

MSCs

No studies to date have been published on the use of MSCs administered via epidural placement.

Sacroiliac Joint

Table 4a-b: Sacroiliac Joint Orthobiologic Studies

PRP

Table 4a summarizes the characteristics and results of the currently available studies regarding sacroiliac joint PRP. There is one level I study that demonstrated significant improvement from baseline after both sacroiliac joint (SIJ) PRP as well as steroid injection with triamcinolone at 3 months. Patients in the PRP group maintained 90% efficacy at 3 months while the steroid group maintained 25% efficacy. Modified ODI and SF-12 gradually improved in the PRP group through 3 months while the steroid group demonstrated initial improvement at 4 weeks with subsequent deterioration at 3 months.[70] Additionally, there are two level IV studies that demonstrated significant pain reduction at one year, with one study demonstrating sustained clinical benefits through four years.[71,72] Noteworthy, Ko et al. injected PRP at Hacketts points A, B, and C (posterior SI ligaments). Although their target was not truly intraarticular SIJ, the decision was made to include this study within the review because of the proximity of the posterior SI ligaments to the actual SIJ and the likelihood, given the high number of injections utilized, that some PRP was actually injected within the SIJ. This should be taken into account when interpreting their results.[71]

Prolotherapy

Table 4b summarizes the characteristics and results of the currently available studies regarding sacroiliac joint prolotherapy. There is one level I study that compared SIJ injections with prolotherapy versus steroid which found a significant difference with regard to achieving greater than or equal to 50% pain relief at 15 months post procedure, 58.7% for prolotherapy group and 10.2% for the steroid group.[73] Additionally, there is one level III study that found 23% of patients achieved an minimal clinically important difference in ODI at 4 months following 3 SIJ prolotherapy injections.[74]

MSCs

No studies to date have been published on the use of MSCs administered via the sacroiliac joint.

4. CONCLUSIONS & FUTURE RESEARCH RECOMMENDATIONS

We aimed to provide the reader with a clinical perspective on the existing orthobiologic literature for spine-related pain. At the time of this publication there is one level I study that demonstrated positive results for each of the following, PRP and MSCs for discogenic pain, facet PRP, epidural autologous conditioned serum, as well as PRP and prolotherapy for sacroiliac joint pain. Notably no intervention has multiple published level I studies. In order to verify these findings, it is paramount that additional level I studies are conducted to replicate these positive results. The one level I study on facet prolotherapy found no significant benefit. It is important to remember the non-standard injectate used for this study. The one level I study on epidural prolotherapy found a significant difference in pain scores at 48 hours compared to the control group, but no significant difference at the two-week endpoint. Thus far the studies for intradiscal prolotherapy and epidural PRP are limited to no higher than level III. MSCs have yet to be analyzed for any pain generator aside from the intervertebral disc.

Additional studies on spine-related pain are now being published at increasing rates as the science behind and evidence for regenerative medicine continues to expand for other musculoskeletal ailments.[12] Of the 35 reviewed articles, 25 have been published in the last five years. However, to support continued use, limitations in the current literature must be acknowledged and accounted for in future studies. As with all emerging therapies, a paucity of high-quality evidence hinders widespread acceptance. Additional level I/II/III studies should be prioritized. The vast majority of current studies have no comparative group. A starting point going forward would be to compare cohorts of patients treated with regenerative medicine to those treated with “standard of care”.

Amongst all regenerative therapeutics evaluated, preparation consistency and reporting were severely lacking. Standardization of preparation reporting is a viable first step, classification systems such as PLRA for PRP are a shining example and additional systems for MSCs are needed. This will allow for better protocol reproducibility and improved comparison of treatment efficacy, which is currently precluded given the wide variability in existing literature.

In light of this large heterogeneity amongst orthobiologic preparation, injectate delivery method, location, and number of treatments, as well as the paucity of well-designed randomized controlled trials the authors opted to present the current literature in the form of a narrative review. A few systematic reviews do exist in the literature on this topic.[75-78] Having said that, in the absence of improved standardization regarding the aforementioned points, the authors felt a narrative review that included the three most common orthobiologic agents used in the treatment of axial/radicular spine pain and the similarities/differences amongst the currently available studies would be most suitable for assistance when interpreting the current literature.

As the current landscape of medicine continues to evolve and regenerative interventions increasingly become a part of the dialogue between patients and providers, it is paramount that we continually review the most up to date evidence regarding the therapies and interventions we have to offer. This evidence-based approach to interventional selection provides the patient with both the greatest likelihood of success, as well as demonstrates a responsibility of resources on the part of the provider. Our hope would be that this approach will help to maintain the durability of long-term access to these orthobiologic therapies and make them more accessible through insurance authorization.

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Table 1a: Discogenic Orthobiologic Studies – PRP

PRP					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Tuakli-Wosornu[34] (2016)	I	Design: Prospective double blinded randomized controlled trial Intervention: PRP vs Contrast Control Sample Size: 47 [29 PRP] Follow up: 12 mo	P: 3-4mL L: NR R: NR A: NR Control: 3-4mL Omnipaue 180 contrast agent	Significant improvement in PRP group at 8 weeks regarding pain (NRS), function (FRI), and satisfaction (NASS Outcome Questionnaire). At 1 year PRP group had significant improvements in NRS Worst Pain, FRI, and SF-36 Pain (outcomes vs control not evaluated after 8 weeks).	NRS SF-36 Pain
Akeda[35] (2017)	IV	Design: Prospective clinical feasibility study Intervention: PRP Sample Size: 14 Follow up: 10 mo	P: 2mL 907 x 10^3/uL L: - R: + A: + (CaCl2)	Significant improvement in VAS at 1 month that was sustained through follow-up ~10 mo.	VAS
Navani[39] (2018)	IV	Design: Case series Intervention: PRP or BMAC-MSC x1, 1-3 discs Sample Size: 15 Follow up: 18 mo	P: 1-2mL L: NR R: NR A: - BMAC-MSC: 1-2mL	>50% relief in VPS in 94% of patients at 6 months, and in 93% of patients at 18 months. SF-36s physical component summary was improved in 100% of patients at 6 months, and in 93% of patients at 18 months. Medication use decreased in 89% of patients at 6 months and in 80% of patients at 18 months.	VPS SF-36
Kirchner[38] (2016)	IV	Design: Observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, & 1 transforaminal epidural injection of PRGF-Endoret Sample Size: 86 Follow up: 6 mo	P: 4mL (2x peripheral blood) L: NR R: NR A: + PRGF activator (CaCl2)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS
Levi[37] (2016)	IV	Design: Prospective trial Intervention: PRP x1, 1-5 discs Sample Size: 22 Follow up: 6 mo	P: 0.5-1.5mL L: + R: NR A: NR	Success determined by 50% or greater improvement in VAS and 30% decrease in ODI. Categorical success rates as follows: 14% at 1 month, 32% at 2 months, and 47% at 6 months.	VAS ODI

Comella[36] (2017)	IV	Design: Open label Intervention: PRP/SVF x1, 1+ discs Sample Size: 15 Follow up: 6 mo	SVF (ASC + GFs) PLUS: P: 1mL L: NR R: NR A: NR	Statistically significant improvement in VAS, PPI, SF-12, and flexion at 6 months. Additionally both ODI and BDI data was trending positive and a majority of patients reported improvements in their Dallas Pain Questionnaire scores.	VAS, PPI, ODI, and SF-12

Key: PRP = platelet rich plasma; P = platelet count; L = leukocyte content (+ = >1%; - = <1%); R = red blood cell content (+ = >1%; - = <1%); NR = not reported; A = activation (+ = yes; - = no); NRS = numerical rating scale; FRI = functional rating index; SF-36 = 36 item short form health survey; VAS = visual analogue scale; BMAC = bone marrow aspirate concentrate; MSC = mesenchymal signaling cells; VPS = verbal pain scale; PRGF = plasma rich in growth factors; ODI = oswestry disability index; SVF = stromal vascular fraction; ASC = adipose signaling cells; GF = growth factors; NR = not reported; PPI = present pain intensity; SF-12 = 12 item short form health survey; BDI = beck depression inventory

Table 1b: Discogenic Orthobiologic Studies – Prolotherarpy

Prolotherapy					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Miller[41] (2006)	IV	Design: Prospective case series. Intervention: Bi-weekly hypertonic dextrose (avg 3.5 inj) Sample Size: 76 Follow up: 18 mo	50% dextrose	33 (43.4%) achieved sustained improvement group with an average improvement in NPS of 71% at 18 mo. 37 (48.7%) non-responders (<20% pain reduction); 6 temporary (<2 months) responders.	NPS
Derby[40] (2004)	III	Design: Pilot study Intervention: IDET vs hypertonic dextrose / DMSO./ glucosamine / chondroitin sulfate Sample Size: 109 [34 prolo] Follow up: IDET avg 15.5 mo & Prolo 7.7 mo	50% Dextrose + 0.5% chondroitin sulfate + 20% glucosamine hydrochloride + 12% DMSO + 2% bupivacaine.	Pain relief was statistically significant for both procedures, but slightly better for injections (2.2 VAS) than for IDET (1.27 VAS), (p=0.01). Patients receiving injections were significantly more satisfied with the results of treatment. Only 47.8% of IDET patients reported that they felt better, whereas 65.6% of injection patients reported this outcome. Among IDET patients, 35.8% reported they were worse, while no restorative injection patient reported worsening of pain. Post-procedure flare-up occurred more frequently after restorative injection (81%) than after IDET (68.9%) and was more severe (7.9 versus 6.1 VAS, respectively). Duration of pain flare-up was notably shorter for restorative injections (8.6 days) than for IDET (33.1 days).	VAS, satisfaction rate, and flare up before and after the procedures

Key: NPS = numerical pain score; IDET = intradiscal electrothermal annuloplasty; DMSO = dimethylsulfoxide; VAS = visual analogue scale

Table 1c: Discogenic Orthobiologic Studies – MSC

MSC					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Noriega[42] (2017)	I	Design: RCT Intervention: BMAC-MSC vs Sham paravertebral muscular injection Sample Size: 24 [12 MSC] Follow up: 12 mo	Allogenic BMAC (25 × 10^6 MSC in 2mL of saline per disc) Control: 2mL of 1% mepivacaine	Significant improvement in VAS and ODI at 3 months that was sustained through 12 months. There was no significant improvement observed in the control group.	VAS, ODI, SF-12, MRI
Pettine[43] (2017)	IV	Design: Prospective, open-label, non-randomized, single-arm study Intervention: BMAC-MSC Sample Size: 26 Follow up: 3 yrs	2-3mL of Autologous BMAC (2702/mL mesenchymal cell concentration)	77% of treatment group had significant improvement in VAS and ODI sustained through 36 months. MRI at 1 year demonstrated one modified Pfirrmann Grade improvement in 18/20 patients and no worsening on MRI.	VAS, ODI, MRI
Orozco[44] (2011)	IV	Design: Pilot phase I trial Intervention: Autologous expanded BMAC MSC Sample Size: 10 Follow up: 12 mo	Autologous BMAC (23±5×10^6 MSCs)	Significant improvement in VAS and ODI at 3 months that was sustained through 12 months. 85% of total improvement occurred in the first 3 months. Additionally, disc water content was significantly increased at 12 months, though no significant increase in disc height.	VAS, ODI, MRI
Coric[48] (2013)	IV	Design: Phase I investigational new drug single-arm, prospective feasibility study Intervention: Allogenic juvenile chondrocytes x1 Sample Size: 15 Follow up: 12 mo	Culture-expanded allogenic juvenile chondrocyte cells (10^7 cells/mL + fibrin carrier)	Mean ODI, NRS, and SF-36 overall significantly improved from baseline. Of the 9 patients with HIZ at baseline, 8 (89%) either showed improvement or resolution at 6 months (the 9th showed improvement at 3 months without further follow up). 10 (77%) of 13 patients with follow up MRI at 6 months demonstrated improvement with 8 of 10 sustaining or continued improvement at 12 months.	ODI, NRS, SF-36, MRI

Mochida[49] (2015)	IV	Design: Prospective clinical study Intervention: NP chondrocytes + autologous BMAC-MSC in adjacent fusion level post-op day 7 Sample Size: 9 Follow up: 3 years	Autologous NP chondrocytes cocultured with BMAC-MSCs (1×10^6 cells/702 µL sterile saline)	Viable NP cells from the fused disc were co-cultured in direct contact with autologous bone marrow-derived MSCs. One million activated NP cells were transplanted into the degenerated disc adjacent to the fused level at 7 d after the first fusion surgery. Significant improvement in JOA pain scores at 36 months compared to baseline. Injection occurred 7 days after fusion surgery.	JOA, MRI
Kumar[47] (2017)	IV	Design: Single-arm, open-label, phase I clinical trial Intervention: ADSCs + HA x1 Sample Size: 10 Follow up: 12 mo	Culture-expanded ADSCs + HA derivative (2 × 10^7 cells/disc (n = 5) or 4 × 10^7 cells/disc (n = 5))	Significant improvement in VAS, ODI and SF-36 in both groups (low and high cell doses) without difference between groups. 6 (60%) of patients achieved treatment success with pain reduction 50% or greater, improved ODI, and SF-36. 3 of these 6 additionally had improved disc water content.	VAS, ODI, SF-36, MRI, X-ray
Haufe[46] (2006)	IV	Design: Prospective case series Intervention: BMAC-MSC x1 Sample Size: 10 Follow up: 12 mo	1mL BMAC MSC + hyperbaric O2 treatment (cell count not reported)	No significant improvement in back pain at 12 months.	Pain Score
Centeno[45] (2017)	IV	Design: Pilot study Intervention: 2 wks pre-tx, 3-5 cc TFEI of autologous PL at affected disc level. Treatment, BMAC-MSC + PL 10-20%. 2 wks post-tx, 3-5 cc TFEI of autologous PL at affected disc level. Sample Size: 33 Follow up: 6 yr	1-3mL culture-expanded, autologous, BMAC MSCs + autologous PL 10–20%. (cell count not reported)	NPS scores relative to baseline were significant at 3, 36, 48, 60, and 72 months post-treatment. The average modified SANE ratings showed a mean improvement of 60% at 3 years post-treatment. FRI post-treatment change score averages exceeded the minimal clinically important difference at all time points except 12 months. Twenty of the patients treated underwent post-treatment MRI and 85% had a reduction in disc bulge size, with an average reduction size of 23% post-treatment.	NPS, a modified SANE, FRI, measurement of the intervertebral disc posterior dimension, and adverse events.

Key: RCT = randomized controlled trial; HIZ = high intensity zone; NP = nucleus pulposus; JOA = Japanese orthopaedic association score; ADSCs = adipose derived signaling cells; HA = hyaluronic acid; TFESI = transforaminal epidural steroid injection; PL = platelet lysate; SANE = single assessment numerical evaluation; NRS = numerical rating scale; NPS = numerical pain scale; FRI = functional rating index; SF-36 = 36 item short form health survey; VAS = visual analogue scale; BMAC = bone marrow aspirate concentrate; MSC = mesenchymal signaling cells; ODI = oswestry disability index; SF-12 = 12 item short form health survey

Table 2a: Facet Orthobiologic Studies - PRP

PRP					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Wu[50] (2017)	I	Design: Prospective randomized controlled study Intervention: PRP vs LA/CS Sample Size: 46 [23 PRP] Follow up: 6 mo	P: 0.5mL 100-300x10^9/mL L: NR R: - A: NR Control: 0.5mL of 0.5% lidocaine and 5mg/mL betamethasone (4:1)	Significant improvement in VAS, RMQ, and ODI in both groups at 1 month, only PRP group sustained improvement at 6 months.	VAS ODI RMQ
Wu[51] (2016)	IV	Design: Prospective series Intervention: Autologous PRP Sample Size: 19 Follow up: 3 mo	P: 0.5mL 100-300x10^9/mL L: NR R: NR A: NR	Significant improvement in VAS at rest and with flexion, RMQ, and ODI at 3 months. 79% with outcomes assessed as "excellent" at 3 months.	VAS ODI RMQ
Kirchner[38] (2016)	IV	Design: Observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, & 1 transforaminal epidural injection of PRGF-Endoret Sample Size: 86 Follow up: 6 mo	P: 4mL (2x peripheral blood) L: NR R: NR A: + PRGF activator (CaCl2)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS
Aufiero[52] (2015)	IV	Design: Case series Intervention: Series of 3 PRP facet + ligament injections Sample Size: 5 Follow up: 6-12 mo	P: >1.5x10^6 L: - R: - A: -	All reported symptom relief and decrease in VAS at follow-up. Case 1: 100%improvement & return to sport at 6 months.Case 2: 1/10 VAS score at 9 months.Case 3: 2/10 VAS score and improvement in functional status at 12 months.Case 4: 70% symptom improvement & increased functional status after series of 3. Case 5: 65-70% symptom improvement and increased functional status at 6-month follow-up.	VAS

Key: PRP = platelet rich plasma; P = platelet count; L = leukocyte content (+ = >1%; - = <1%); R = red blood cell content (+ = >1%; - = <1%); NR = not reported; A = activation (+ = yes; - = no); LA = local anesthetic; CS = corticosteroid; RMQ = roland-morris disability questionnaire; VAS = visual analogue scale; PRGF = plasma rich in growth factors; ODI = oswestry disability index; NR = not reported

Table 2b: Facet Orthobiologic Studies - Prolotherapy

Prolotherapy					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Dechow[53] (1999)	I	Design: Randomized, double-blind, placebo-controlled trial Intervention: Lumbar prolo+ (3 injections) + iliolumbar / SI ligaments Sample Size: 74 Follow up: 6 mo	Treatment: 5mL 25% dextrose / 25% glycerine / 2.4% phenol + 5mL 1% lignocaine Control: 5mL NS + 5mL 1% lignocaine	No statistically significant difference in pain outcomes at 6 months in treatment versus control group. Both groups demonstrated a downward trend but did not reach statistical significance.	SF-MPQ
Hooper[54] (2011)	III	Design: Prospective case series Intervention: C/T/L Prolo +/- iliolumbar/SI ligaments (3-6 inj) Sample Size: 147 Follow up: 12 mo	0.5mL 20% dextrose + 0.75% lidocaine	Both litigants (71) and non-litigants (76) showed significant improvement from baseline on all disability scales ($P < 0.001$). There were no differences in the percentage of litigants/non-litigants reporting improvement on impression of change scales for symptoms (91/92%), function (90/90%), improved ability to work (76/75%), willingness to repeat treatment (91/93%), ability to decrease medication (82/81%), and decreased need for other treatment (80/84%).	NDI, Patient Specific Functional Scale, and RMQ
Hooper[55] (2004)	IV	Design: Retrospective case series Intervention: C/T/L Prolo +/- iliolumbar/SI ligaments (3-6 inj) Sample Size: 177 Follow up: 2 mo - 2.5 yrs	0.5mL 20% dextrose + 0.75% lidocaine	91% of patients reported reduction in level of pain; 85% of patients reported improvement in activities of daily living, and 84% reported an improvement in ability to work.	NPS

Hooper[56] (2007)	IV	Design: Case series Intervention: B/l 3 level C-spine Prolotherapy Sample Size: 15 Follow up: 12 mo	0.5-1mL 20% dextrose + 1% lidocaine	Mean NDI pre-treatment was 24.71 and decreased post-treatment to 14.21 (2 months), 13.45 (6 months), 10.94 (12 months). Average change NDI=13.77 ($p<0.0001$) baseline versus 12 months.	NDI

Key: SI = sacroiliac; SF-MPQ = short form mcgill pain questionnaire; NDI = neck disability index; RMQ = roland-morris disability questionnaire; NPS = numerical pain scale; C/T/L = cervical/thoracic/lumbar

Table 3a: Epidural Orthobiologic Studies - PRP

PRP					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Becker[57] (2007)	I	Design: P-DB-Ref CT Intervention: ACS vs 5mg or 10mg Triamcinolone Sample Size: 84 Follow up: 6 mo	IL-1 receptor antagonist (RA)-enriched ACS Control: 5mg or 10mg of triamcinolone	All 3 groups with clinically remarkable and statistically significant reduction in VAS and ODI. ACS with consistent pattern of superiority to triamcinolone from week 12 to final evaluation at week 22 in VAS. No statistically significant difference between the 2 triamcinolone dosages during the study period.	VAS ODI
Correa[59] (2019)	IV	Design: Prospective observational, non-randomized Intervention: C / L spine PRGF x2 Sample Size: 250 Follow up: 2 yrs	PRGF P: 10-12mL L: NR R: NR A: NR	Significant improvement in VAS and MACNAB through two years of follow-up.	VAS mMACNAB
Centeno[58] (2017)	IV	Design: Prospective registry Intervention: Platelet Lysate (PL) Sample Size: 470 Follow up: 2 yrs	3-5mL PL 50%, 4% lidocaine 25%, and compounded preservative free 100–200 ng/ml hydrocortisone 25%.	Post PL treatment, significantly lower ($p < .0001$) NPS and FRI change scores at all time points compared to baseline. Post-treatment FRI change score means exceeded the minimal clinically important difference beyond 1 month. Average modified SANE ratings showed 49.7% improvement at 24 months post-treatment. Twenty-nine (6.3%) patients reported mild adverse events related to treatment.	NPS FRI SANE
Kumar[61] (2015)	IV	Design: Case series Intervention: ACS (1-3 inj) Sample Size: 20 Follow up: 6 mo	2mL IL-1 RA-enriched ACS	Statistically significant change in quadruple VAS, RODI, SF-12 from pre-injection to first, second, and third follow-up ($p<0.001$).	VAS
Kirchner[38] (2016)	IV	Design: Observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, & 1 transforaminal epidural	P: 4mL (2x peripheral blood) L: NR R: NR A: + PRGF activator ($CaCl_2$)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS

		injection of PRGF-Endoret Sample Size: 86 Follow up: 6 mo			
Bhatia[60] (2016)	IV	Design: Case Series Intervention: PRP x1 Sample Size: 10 Follow up: 3 mo	P: 5mL L: NR R: NR A: NR	All showed improvement in VAS, SLRT and MODI index which was sustained at 3 months. 90% had VAS ≤ 4 at 3 months.	VAS

Key: ACS = autologous conditioned serum; PRP = platelet rich plasma; P = platelet count; L = leukocyte content (+ = >1%; - = <1%); R = red blood cell content (+ = >1%; - = <1%); NR = not reported; A = activation (+ = yes; - = no); NPS = numerical pain scale; SANE = single assessment numerical evaluation; FRI = functional rating index; VAS = visual analogue scale; PRGF = plasma rich in growth factors; rODI = revised oswestry disability index; NR = not reported; SF-12 = 12 item short form health survey; mODI = modified oswestry disability index; SLRT = straight leg raising test; C/L = cervical/lumbar

Table 3b: Epidural Orthobiologic Studies - Prolotherapy

Prolotherapy					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Maniquis-Smigel[62] (2016)	I	Design: RCT Intervention: Caudal prolotherapy vs NS control x1 Sample Size: 35 [19 prolo] Follow up: 2 wks	10mL 5% Dextrose Control: 10mL 0.9% NS	Significant difference in NRS pain score up to 48 hours but not at 2 weeks. 84% (16/19) of dextrose recipients and 19% (3/16) of saline recipients reported ≥ 50% pain reduction at 4 hours.	NRS
Maniquis-Smigel[63] (2018)	IV	Design: Prospective uncontrolled Intervention: Caudal prolotherapy (5.5 ± 2.9 inj) Sample Size: 32 Follow up: 1 yr	10mL 5% Dextrose	Compared with baseline status, NRS and ODI scores improved by 3.4 ± 2.3 (52%) and 18.2 ± 16.4% (42%) points, respectively ($p<0.001$) at 1 year. The fraction of participants with 50% reduction in NRS-based pain was 21/32 (66%).	NRS

Key: NS = normal saline; NRS = numerical rating scale; ODI = oswestry disability index; RCT = randomized controlled trial

Table 4a: Sacroiliac Joint Orthobiologic Studies – PRP

PRP					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Singla[59] (2017)	I	Design: Prospective randomized open blinded end point (PROBE) study. Intervention: PRP vs Steroid Sample Size: 40 Follow up: 3 mo	Group P: P: 3mL L: - R: NR A: 0.5mL CaCl2 Group S: 3mL methylprednisolone (40 mg/mL) with 2% lidocaine and saline	Pain significantly less at 6 weeks and 3 months in group P vs S. The efficacy of steroid injection was reduced to only 25% at 3 months in Group S, while it was 90% in Group P. A strong association was observed in patients receiving PRP and showing a reduction of VAS ≥ 50% from baseline when other factors were controlled. The mODI and SF-12 scores were improved initially for up to 4 weeks but deteriorated further at 3 months in Group S, while both the scores improved gradually for up to 3 months in Group P.	VAS, mODI, SF-12
Ko[60] (2017)	IV	Design: Case Series Intervention: Hackett's points A, B, & C inj x 2 Sample Size: 4 Follow up: 4 yrs	P: 10mL (5-6x > baseline) L: NR R: NR A: NR 0.5ml with each needle contact of the ligament-bone interface at Hackett's Points A, B, and C.	Clinically and statistically significant reduction in pain at 1-year post treatment, as evidenced by a 93%, 88%, and 75% reduction in the mean SFMPQ ($P < 0.0001$), NRS ($P < 0.001$) and ODI ($P < 0.0001$) scores respectively. The clinical benefits of PRP were still significant at 4-years post-treatment. Additionally, patients achieved an improvement in their quality of life, and returned to their pre-injury statuses.	SFMPQ, NRS, ODI
Navani[61] (2015)	IV	Design: Case series Intervention: PRP x1 Sample Size: 10 Follow up: 12 mo	P: 4mL L: NR R: NR A: NR	VAS score for all patients decreased more than 50% and their function increased for the period of 12 months.	VAS, SF-36

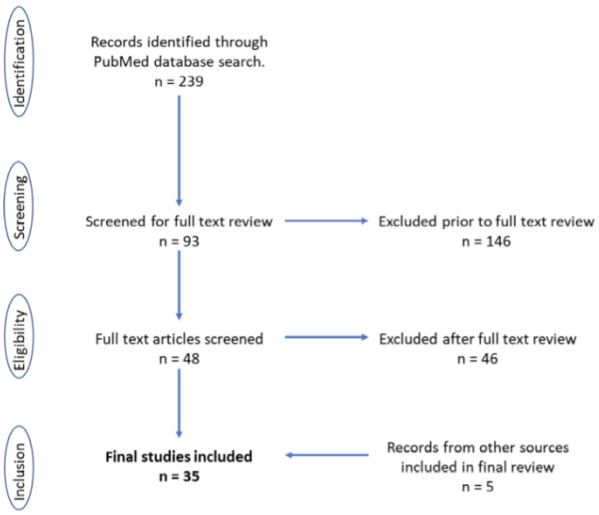
Key: PRP = platelet rich plasma; P = platelet count; L = leukocyte content (+ = >1%; - = <1%); R = red blood cell content (+ = >1%; - = <1%); NR = not reported; A = activation (+ = yes; - = no); VAS = visual analogue scale; mODI = modified oswestry disability index; SF-12 = 12 item short form health survery; NRS = numerical rating scale; SF-36 = 36 item short form health survery; SFMPQ = short form mcgill pain questionnaire; NR = not reported

Table 4b: Sacroiliac Joint Orthobiologic Studies – Prolotherapy

Prolotherapy					
Author, year	**Level of Evidence**	**Study Details**	**Composition**	**Results**	**Pain Outcome Measures**
Kim[62] (2010)	I	Design: RCT Intervention: Bi-weekly prolotherapy vs steroid, max 3 inj. Sample Size: 48 [23 prolo] Follow up: 15 mo	2.5mL 25% Dextrose	Both groups NRS and ODI significantly improved from baseline at 2 weeks, no significant difference between the two. Cumulative incidence of ≥50% pain relief at 15 months was 58.7% for prolotherapy group vs 10.2% in steroid group. Statistically significant difference between the two at 15 months.	NRS ODI
Hoffman[63] (2018)	III	Design: Retrospective cohort study. Intervention: Prolotherapy x3 (1 mo intervals) Sample Size: 103 Follow up: ~4 mo	15% dextrose (3mL 50% dextrose + 7mL 1% lidocaine)	24 (23%) achieved ≥15 point ODI improvement (ie achieved MCID), 29 (28%) had ODI improvement <15 points, and in 50 (49%) of patients ODI was unchanged or worsened. 15-point improvement in ODI prior to the second prolotherapy injection had a sensitivity of 92% and specificity of 80% for determining which patients would improve.	ODI

Key: RCT = randomized controlled trial; NRS.= numerical rating scale; ODI = oswestry disability index; MCID = minimal clinically important difference

Figure 1: Flowchart of study inclusion



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