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Review Article

The Effectiveness of Platelet-Rich Plasma Injection for the Treatment of Suspected Sacroiliac Joint Complex Pain; a Systematic Review

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Abstract

Objective. To determine the effectiveness of platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) for the treatment of suspected sacroiliac joint complex (SIJC) pain. **Design**. Systematic review. **Subjects**. Persons aged ≥18 with suspected SIJC pain. **Comparison**. Sham, placebo procedure, or active standard of care treatment. **Outcomes**. The primary outcome was ≥50% pain improvement, and the secondary outcome was functional improvement of ≥30% at three or more months after the treatment intervention. **Methods**. Publications in PubMed, MEDLINE, Embase, Scopus, and Cochrane Databases were reviewed up to April 3, 2019. Randomized or nonrandomized comparative studies and nonrandomized studies without internal controls were included. The Grades of Recommendation, Assessment, Development, and Evaluation system and the joint consensus American Academy of Orthopedic Surgery/National Institutes of Health recommendations were used for quality assessment and reporting standards. **Results**. Query identified 151 publications; three were appropriate for inclusion. There were no studies of BMAC that met inclusion criteria. There were three eligible PRP studies: one randomized comparative trial (RCT) and two case series. In the single RCT comparing ultrasound-guided PRP with corticosteroid injection for suspected SIJC pain, the PRP group had a significantly increased likelihood of achieving ≥50% improvement of pain at three months (adjusted odds ratio = 37, 95% confidence interval [CI] = 4.65–298.69). Pooled pain outcomes from two studies showed that 28/30, 93% (95% CI = 93–100%), experienced ≥50% pain improvement at three months. **Conclusions**. The literature supporting the effectiveness of PRP for SIJC pain is very low-quality according to the GRADE system. Well-designed RCTs and large cohort studies with consistent selection protocols and reporting characteristics are needed to determine the effectiveness of PRP and BMAC for the treatment of SIJC pain.

Key Words: Sacroiliac Joint; Platelet-rich Plasma

Introduction

Within the population of those with suspected sacroiliac joint complex (SIJC) pain, 10–15% experienced diagnostic pain relief after intra-articular (IA) block with an anesthetic. The incidence is thought to be higher in patients with prior lumbar fusion or pelvic trauma [1–5]. The SIJC is composed of two different structures: the sacroiliac joint (SIJ) and the posterior sacroiliac joint ligaments (PSIJLs) [6,7]. The SIJ and PSIJLs have overlapping but different sensory innervation; the SIJ is thought to be primarily innervated anteriorly by the lumbosacral trunk, obturator nerve, superior gluteal nerve, and L4 and L5 ventral rami [8–10], with some posterior innervation by the lateral branches of the S1–S3 dorsal rami and fibers of the L5 dorsal ramus [8,11]. The PSIJLs are primarily innervated by the sacral lateral branches (LBs) of S1–S3

with some innervation from the L5 and S3 LBs [9,12]. Definitive diagnosis of SICJ pain has proven difficult, and the predictive power of physical exam findings, intra-articular (IA) SIJ blocks, and sacral lateral branch blocks (SLBBs) has been variable [6,13–15].

Although frequently utilized, there are no data on conservative treatments such as activity modification, exercise, physical therapy, or oral medications for those with confirmed SIJC pain. Corticosteroid injections into the SIJ may help but are typically short-lived and are often associated with unwanted side effects [16–19]. One study showed longer pain relief after an SIJ steroid injection in patients who were stratified by initial anesthetic response [15]. Repeated steroid injections have been shown to decrease bone mineral density and suppress the hypothalamic-pituitary-adrenal axis [20,21]. This has created a need for other nonsurgical options, such as LBRFA. The present literature indicates that ~50% of patients experience 50% pain relief three months post-RFA [6,22]. Thus, a significant proportion of patients with refractory SIJC pain remain without an ideal treatment option. While appropriate selection protocols and procedural technique improvements for LBRFA will likely improve the success rates of this treatment, the intricate and anterior innervation of the SIJ inaccessible to RFA limits this treatment option for patients with an anterior contribution to their SIJC pain.

There is a growing body of research in the area of biologics as possible nondestructive treatment options. There are currently multiple biologic agents in use, including platelet-rich plasma (PRP) [23], bone marrow aspirate concentrate (BMAC) [24], adipose [25], embryonic stem cells [26], amniotic fluid/membrane [27], and culture-expanded tissue-derived cell (also known as mesenchymal stem cells or mesenchymal stromal cells [MSCs]); these agents have been used in attempts to treat a myriad of musculoskeletal conditions [24,28–32]. The Food and Drug Administration (FDA) has established regulations regarding the use of human cells and tissues, which dictate that human cells and tissues may be used if they are autologous, minimally manipulated, and are used during the same surgical procedure, and are not combined with another product [33]. However, the state of the current evidence is poorly defined, particularly with regard to the treatment of SIJC pain using biologic agents. To date, there has been no systematic review evaluating the effectiveness of PRP or BMAC for the treatment of SIJC pain. The authors' interpretation of the FDA's statement regarding the use of human biologics is that PRP and BMAC are the only agents listed in compliance with these regulations. Therefore, we designated the focus of this review on the use of PRP and BMAC for the treatment of suspected SIJC pain.

Objectives and Rationale

The present study is a systematic review of the published literature on the effectiveness of PRP and BMAC for the treatment of suspected SIJC pain compared with sham, placebo, other active treatments, or no treatment, in terms of pain reduction and disability. This work is anticipated to facilitate understanding among patients, physicians, and regulatory agencies regarding the expected therapeutic value of PRP and BMAC in the treatment of SIJC pain, as well as to identify deficiencies in the current knowledge base that warrant further research.

Methods

Protocol and Registration

This institutional review board–exempt study was registered on PROSPERO (ID: CRD42018107228, 10/15/2018).

Eligibility Criteria

Population. Adults aged ≥18 with suspected SIJC pain.

Intervention. PRP or BMAC injection into the SIJC.

Comparison. Sham, placebo, active treatment, or standard of care treatment.

Outcome. The primary outcome of interest was patient-reported improvement in pain of ≥50% from baseline at three or more months after treatment [34,35]. Functional improvement of ≥30% at three or more months was a secondary outcome [36].

Studies. We considered randomized or nonrandomized comparative studies and nonrandomized studies without internal controls. Case reports, expert opinion, reviews, and unpublished data were excluded. No publication date or language restrictions were enforced.

Information Sources and Search

Clinical outcome studies on the effectiveness of PRP or BMAC for the treatment of suspected SIJC pain were obtained by searching the Medline, Embase, Scopus, and Cochrane databases using the following search terms: (SI joint* OR sacroiliac joint*) AND (stem cell* OR BMAC* or Bone Marrow* OR PRP OR platelet-rich plasma*). The search was designed by DC and performed by TB on April 3, 2019. Literature was also identified from the bibliographies of the retrieved publications.

Study Selection

Two authors (TB and JS) independently assessed each paper meeting the abstract screening criteria. Discrepancies were resolved by consensus discussion. Studies were organized by injectate type (PRP or BMAC) and by which SIJC structure (SIJ and/or PSIJL) was injected.

Data Items and Collection

The following information was extracted from each study: 1) bibliographic details including author, year of publication, and location; 2) study design; 3) participant/patient details/inclusion and exclusion criteria; 4) injury details including method of diagnosis and previous

treatments for current injury; 5) intervention or surgical findings; 6) preprocedural blood work; 7) PRP processing including processing protocol; 8) PRP characteristics; 9) injectate delivery technique; 10) postprocedural care; 11) outcome measures; and 12) complications. These reporting standards were modified from the American Academy of Orthopedic Surgery/National Institutes of Health (AAOS/NIH) consensus recommendations to include characteristics relevant to PRP and BMAC (Table 1) [40].

Risk of Bias and Methodologic Assessment

Four of the authors with formal training in assessment of medical literature and principles of evidence-based medicine (TB, RS, AC, and ZM) assessed the risk of bias of the included studies using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system [41]. Discrepancies were resolved by consensus discussion. Studies were also evaluated for the number of "minimum reporting standards for clinical studies evaluating PRP" according to the consensus recommendations from the joint 2018 AAOS/NIH conference [40].

Summary Measures

The primary summary measures were measures of association (e.g., proportion ratio, relative risk, odds ratio, etc.) using the within-group measure of incidence (proportion of patients reporting $\geq$50% improvement in pain or $\geq$30% improvement in function). The within-group response rate was considered the secondary summary measure. Guidelines have reported the advantage of analyzing categorical data to determine the proportion of the patients who may benefit from an intervention (i.e., responder analysis); in the case of treating SIJC pain, the most commonly used prespecified outcome is $\geq$50% pain relief [6,13,34,42]. Only studies providing categorical data or raw data allowing for calculations of success rates (defined as the proportion of patients with a self-reported $\geq$50% improvement in pain or $\geq$30% improvement in function) were included in the final results.

Synthesis of Results

Regarding internal and external validity, the data of the primary studies were assessed independent of the conclusions of the original authors. The quality of evidence regarding the effectiveness of PRP and BMAC for the treatment of SIJC pain was assessed using the GRADE system. If measures of association could not be calculated, inconsistency across studies was evaluated by confidence intervals [43]. The quality of assessment and outcomes are described in (Table 2). The number of AAOS reporting characteristics, per study, is described in Table 1 [40].

Results

Study Selection

A total of 151 publications were identified from the initial literature search. Titles and abstracts were screened in order to identify relevant publications; 144 potential abstracts were then screened, which yielded seven articles that were selected for potential inclusion based on the study design criteria. Four studies were excluded, resulting in three meeting the inclusion criteria. No study was identified that evaluated the use of BMAC as a treatment option for SIJC pain. Three articles met inclusion criteria. The process of article screening and selection is represented in the Preferred Reporting in Systematic Reviews and Meta-Analysis (PRISMA) flow diagram (Figure 1).

Of the three studies that met the established inclusion criteria, one was a prospective randomized, open blinded end point (PROBE) study and two were case series. Studies were then stratified by target SIJC structure, SIJ or PSIJL, and are described in Tables 1 and 2.

Injectate Type: PRP

Sacroiliac Joint Complex Target: Sacroiliac Joint

In 2017, Singla et al. published an open-label, single-center, randomized prospective trial evaluating the outcomes of ultrasound-guided intra-articular (IA) SIJ injections of PRP vs methylprednisolone in patients suffering from suspected SIJC pathology [37]. The diagnosis of SIJ pain was made based on unilateral SIJ pathology on x-ray, magnetic resonance imaging (MRI), or nuclear scan, along with at least three positive SIJ provocation tests (sacral thrust, iliac distraction, iliac compression, thigh thrust, Patrick's test, and Gaenslen's test). The diagnosis was not based on response to IA SIJ or SLBBs with anesthetic. The study population included patients aged 18–65 with chronic low back pain of moderate intensity for at least three months. A total of 40 patients were randomized, 20 per group, to receive 3 mL of leukocyte-free PRP with 0.5 mL of calcium chloride or 1.5 mL of methylprednisolone (40 mg/mL) and 1.5 mL of 2% lidocaine with 0.5 mL of saline. PRP was prepared inside a biosafety cabinet (Imugard III-PL; Terumo Penpol Limited, Thiruvananthapuram, India). No whole-blood (WB) or PRP analysis was performed. The injectate was delivered using a well-described ultrasound-guided technique; however, no images were provided. The primary outcomes were change in visual analog scale (VAS) scores and safety. Secondary outcomes were changes in Modified Oswestry Disability Questionnaire (MODQ) and Short Form (SF-12) Health Survey scores. Follow-up was performed at two weeks, four weeks, six weeks, and three months post-treatment. At three months, 90% (95% confidence interval [CI] = 77–103%) of the PRP group reported at least 50% VAS improvement, compared with 25% (95% CI = 6–44%) in the methylprednisolone group. There was no between-group difference

Table 1. Quality assessment and primary outcomes of studies evaluating the effectiveness of platelet-rich plasma for the treatment of suspected SIJC pain

			Quality Assessment									Summary of Findings					
No. of Studies	Reference	Design	Limitation	Inconsistency	Indirectness	Imprecision	Other	No. in PRP Group	No. in Steroid Group	Review's Definition of Success	Time of Follow-up Assessment	Proportion Achieving Success (95% CI), % PRP Group	Proportion Achieving Success (95% CI), % Control Group	Relative (95% CI)	Initial GRADE Quality Assessment	Final GRADE Quality Assessment	Importance
SIJ																	
1	Singla 2017 [37]	RCT (PROBE)	Very serious*	No serious limitations	No serious limitations	Serious†	Upgraded for large magnitude of effect	20	20	≥50% VAS improvement	3 months	90 (77–103)	25 (6–44)	Adjusted OR= 37 (4.65–298.69)	High	Low	Critical
1	Navani 2015 [38]	Observation (case series)	Very serious‡	No serious limitations	No serious limitations	Very serious§	None	10	0	≥50% VAS improvement	1, 3, 6, 12 mo	100 (100–100)	N/A	N/A	Low	Very low	Critical
PSIJL																	
1	Ko 2017 [39]	Observation (case series)	Very serious‡	Serious¶	Serious‖	Very serious§	None	4	0	Did not meet definition, no raw data provided	1 and 4 y	N/A	N/A	N/A	Low	Very low	Critical

CI = confidence interval; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; PROBE = prospective randomized open blinded end point; PSIJL = posterior sacroiliac joint ligaments; RCT = randomized control trial; SIJ = sacroiliac joint; SIJC = sacroiliac joint complex; VAS = visual analog scale.

*Subjects not blinded.

†Wide CI.

‡No internal control.

§Limited sample size.

¶Not clear patient selection.

‖Not clear PICO.

Table 2. Study evaluation of AAOS-recommended minimum reporting standards for clinical studies evaluation PRP and cell therapies

Year	Reference	Title	Study Design	Injury Details	Recipient Details	Intervention	Whole-Blood Processing	Whole-Blood Characteristics	PRP Processing	PRP Characteristics	Activations	Delivery	Postoperative Care	No. of Reported Characteristic/ Total Minimum Reporting Standards	%
Sacroiliac joint															
RCT															
2017	Singla V, Batra YK, Bharti N, Goni VG, Marwaha N [37]	Steroid vs Platelet-Rich Plasma in Ultrasound-Guided Sacroiliac Joint Injection for Chronic Low Back Pain	1, 1	1, 1, 0	1, 1, 0	1, N/A	1	0	1, 0, 0, 0	1, 0	1	1, 1	1, 1	15 of 23	65
Case series															
2015	Navani A, Gupta D [38]	Role of Intra-articular Platelet-Rich Plasma in Sacroiliac Joint Pain	1, 0	1, 1, 0	1, 1, 0	1, N/A	0	0	0, 0, 0, 0	1, 0	1	1, 1	1, 1	12 of 23	52
Posterior sacroiliac joint ligaments															
Case series															
2017	Ko GD, Mindra S, Lawson GE, Whitmore S, Arseneau L [39]	Case Series of Ultrasound-Guided Platelet-Rich Plasma Injections for Sacroiliac Joint Dysfunction	1, 0	0, 1, 1	1, 0, 0	1, N/A	0	0	0, 0, 0, 0	1, 0	0	1, 1	0, 1	9 of 23	39
Minimum Reporting Standards for Clinical Studies Evaluating Cell Therapies			1. Study design; 2. Relevant institutional and ethical approval /2	1. Diagnosis (grading system and chronicity); 2. Results of any preoperative imaging; 3. Previous surgical or biologic treatments for current injury /3	1. Recipient demographics; 2. Comorbidities; 3.Current anti-inflammatory medications /3	1. Intervention described sufficiently to enable replications; 2. Surgical findings /2	1. Whole-blood storage environment (including concentration and volume of anticoagulant, temperature, and light exposure) /1	1. Whole-blood platelet, differential leukocyte, and red cell analysis of all samples /1	1. PRP processing described sufficiently to enable replications; 2. Platelet recovery rate of protocol; 3. PRP storage temperature and light exposure; 4. Time between blood drawing, PRP processing, activation, and delivery /4	1. PRP format (e.g., liquid, gel, membrane); 2. PRP platelet, differential leukocyte, and red cell analysis of all samples /2	1. Activation described sufficiently to enable replications (volume and concentration of the activating agent) /1	1. Point of delivery; 2. PRP delivery described sufficiently to enable replication /2	1. Rehabilitation protocol sufficiently described to enable replication; 2. Outcome assessments include functional outcomes and recording of complications; if performed radiographic outcomes, physical examination findings, return to activities, and satisfaction /2	/24	

; ^{PRP} =AAOS = American Academy of Orthopedic Surgeryplatelet-rich plasma.

*Each study was given one point for each AAOS characteristic reported. If a specific reporting characteristic was not relevant to the particular study, it was assigned an N/A. Percentages were calculated from total reported characteristics/total relevant AAOS reporting characteristics.

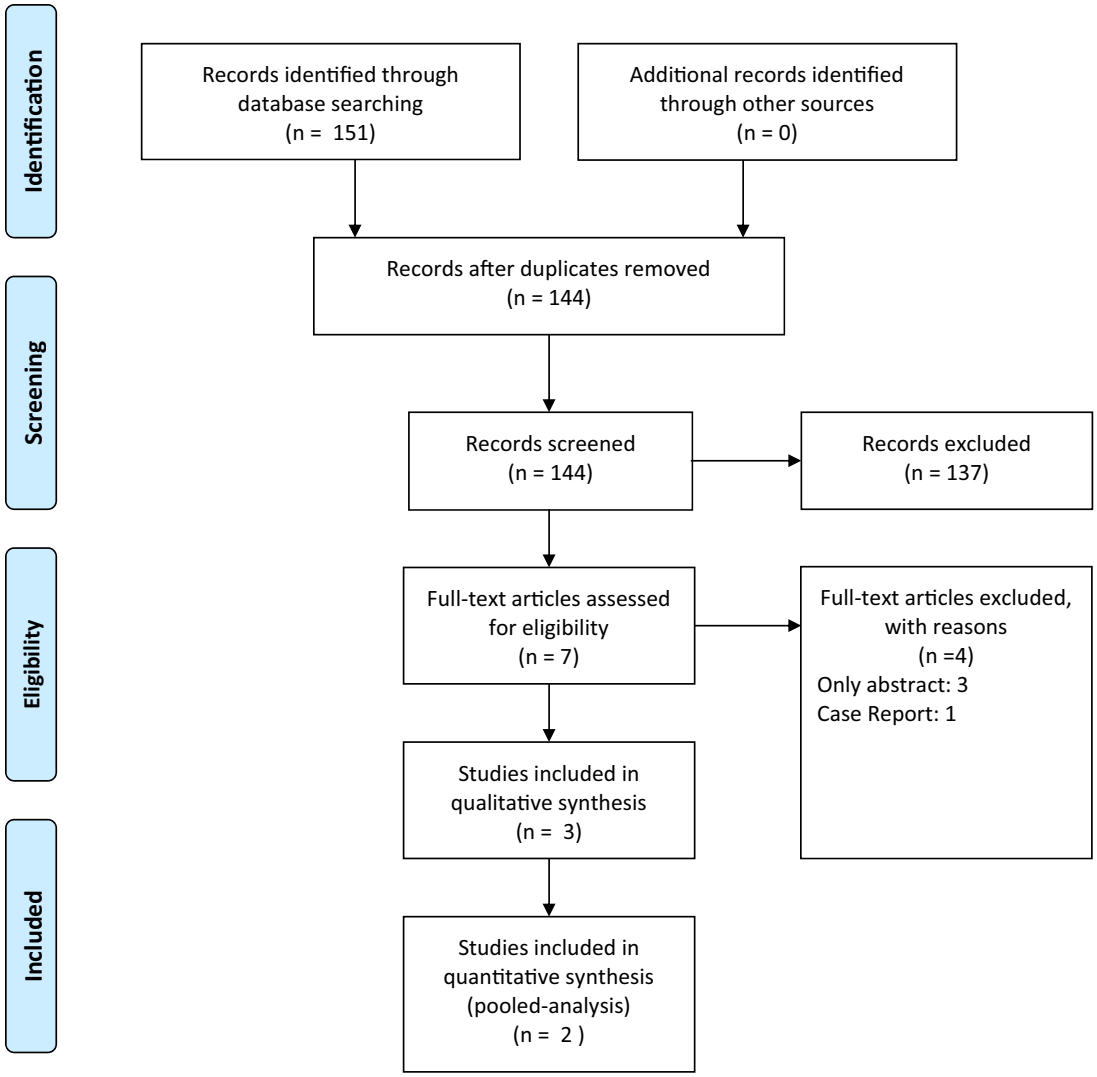

Figure 1.. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram. Source: Moher et al. [44].

in VAS scores at two and four weeks. Intensity of pain was significantly lower in the PRP group at six weeks (median [interquartile range {IQR}] = 1 [1–1] vs 3.5 [2–5], $P = 0.0004$) and three months (median [IQR] = 1 [1–3] vs 5 [3–5], $P = 0.0002$) as compared with the methylprednisolone group. The odds of achieving a reduction in VAS $\geq$50% at six weeks and three months with PRP were 10.91 (adjusted 95% CI = 1.56–76.38, $P = 0.016$) and 37.28 (95% CI = 4.652–298.69, $P = 0.001$), respectively. No raw data were supplied for MODQ and SF-12 changes; the authors reported that MODQ and SF-12 scores improved for up to four weeks but deteriorated further at three months in the methylprednisolone group while both improved in the PRP group. There were no adverse outcomes reported.

In 2015, Navani et al. published a retrospective case series of 10 patients with suspected SIJC pain who received fluoroscopically guided IA SIJ PRP injections [38]. The diagnosis of SIJ pain was based on at least one provocative test (maneuvers not described) and a reported response of >50% pain relief with a single local anesthetic "consistent with the duration of action" ± steroid injection. The authors did not describe anesthetic volume or whether the diagnostic block targeted the SIJ, LBs, or both. The study population included four males and six females with an age range of 30–60. Patients had suffered from LBP for greater than six months and had failed conservative treatment with physical therapy and nonsteroidal anti-inflammatory drugs. The SIJs of all patients were imaged with MRI to evaluate for evidence of inflammation. Eight of the 10 were deemed normal, and two patients had evidence of sclerotic changes and edema. No blood work was reported to confirm an inflammatory diagnosis. Patients underwent a single injection of PRP into the unilateral or bilateral SIJ. The PRP was prepared using a double spin protocol with the EmCyte Corporation centrifuge (Fort Meyers, FL, USA). No WB or PRP analysis was completed. Needle placement was confirmed fluoroscopically without note of contrast usage. Primary outcomes were VAS and SF-36. The secondary outcomes

were additional medical treatments, hospitalizations, and surgery. Follow-up was at one, three, six, and 12 months. The author reported that all patients "decreased more than 50%" on the VAS and "improvement in both physical and mental components" on the SF-36 at a 12-month time point. No raw data were provided for any primary or secondary outcomes at any time point.

Sacroiliac Joint Complex Target: Posterior Sacroiliac Joint Ligaments

In 2017, Ko et al. published a retrospective case series of four patients with suspected SIJC pain who received ultrasound-guided PRP injection into the PSIJL [39]. The diagnosis of SIJC pain was based on patient history, an unspecified number of positive SIJ provocative maneuvers, and inconsistent imaging including x-ray, computed tomography, and MRI. There was no defined selection process for the study population, and diagnosis was not based on response to IA SIJ or SLBBs with anesthetic. Each patient had failed at least one alternative therapy before the study. Patients received ultrasound-guided injections to the PSIJL at Hackett's point A, B, C [45] with a total of 10 mL of PRP prepared using acid citrate dextrose solution during two different sessions at an undefined time interval. PRP was prepared with Harvest Technologies SmartPRep 2 platelet concentrate system. No WB or PRP analysis was completed. Outcomes were change in back pain evaluated on the Short-Form McGill Pain Questionnaire (SFM), numeric rating scale (NRS), and Oswestry Disability Index (ODI). Outcomes were assessed at one and four years post-treatment. Pooled data demonstrated at one year post-treatment a 93%, 88%, and 75% reduction in mean SFM ($P < 0.0001$), NRS ($P < 0.001$), and ODI ($P < 0.0001$), respectively. The results were still significant at four years post-treatment, and the authors also reported an improvement in quality of life. However, no raw data were supplied.

Sacroiliac Complex Target(s): Sacroiliac Joint and Posterior Sacroiliac Joint Ligaments

No studies evaluating the effectiveness of PRP into both the SIJ and PSIJL for the treatment of suspected SIJC were identified.

Adverse Events

There were no serious adverse events reported in any of the included studies.

Synthesis of Results

Only one study had an internal comparison group [37]; thus, a meta-analysis of comparative measure of association was not possible. Patients treated with ultrasound-guided IA SIJ PRP for suspected SIJ pain at three months had an adjusted OR of 37 (95% CI = 4.65–298.69) of achieving ≥50% improvement in pain compared with those treated with intra-articular SIJ steroids. Pooled pain outcomes at three months showed that 93% (95% CI = 93–102%) of patients reported ≥50% pain improvement after treatment of the SIJ with PRP [37,38]. There were no available data that met the authors' defined outcomes regarding pain or function beyond three months. A single retrospective study reported that 100% (95% CI = 100–100%) of patients experienced a ≥50% reduction in pain until the study end point at 12 months [38]. There were no categorical data regarding pain or function at any time point regarding the use of PRP into the PSIJL. Regarding the AAOS cellular therapy recommended reporting characteristics, Singla et al. provided the highest percentage of reporting characteristics at 65%, as seen in Table 2.

Discussion

We report the first systematic review of the effectiveness of PRP and BMAC injection for the treatment of suspected SIJC pain. Published literature on the effectiveness of BMAC injection for the treatment of suspected SIJC pain does not currently exist. Query identified a sparse literature on the effectiveness of PRP injection for suspected SIJC pain. Although seven studies have been published involving PRP to the SIJC, only three met inclusion criteria for this systematic review. Four studies were excluded, as three were published abstracts and one was a case report that had an inadequate description of methodology and results. Based on limited literature, the use of PRP into the SIJ appears to be associated with clinically significant improvement of pain, with ~90% of patients reporting ≥50% symptom improvement up to 12 months. There is no evidence meeting the authors' definition showing the effectiveness of PRP in reducing disability when targeting the PSIJL. The overall confidence in the accuracy of these results must be evaluated in the context of patient selection, procedural accuracy and safety, current knowledge of the active agent, reporting characteristics, and the limited number of studies available. Only one prospective comparative study has been published.

A validated diagnostic or prognostic test should precede patient selection for therapeutic pain interventions. For example, lumbar facet pain is diagnosed, and patients are selected for therapeutic lumbar medial branch radiofrequency ablation (LMBRFA), after experiencing ≥80% pain relief following a dual concordant medial branch block (MBB) with an anesthetic. This criterion decreases false-positive rates and is a predictor of LMBRFA success [46]. Validated diagnostic criteria for SIJC pain are less established and are complicated by the anterior and posterior innervation of the dual structured SIJC (SIJ and PSIL). Multisite, multidepth, dual concordant SLBB with significant pain improvement is the recommended diagnostic criterion for PSIL pain; however, the exact percentage of pain reduction has not been established [14,22,47]. One study used a single

multisite, multidepth SLBB [48], and another study required 75% pain reduction after a single-site dual SLBB [49]. The pain reduction thresholds to define an SLBB procedure as "positive" in the outcome studies included in this systematic review varied from 50% to 75%. Currently, by the GRADE system, there is moderate evidence regarding the validity of SLBBs for the diagnosis of PSIL pain [47]. Ko et al. treated the PSIL with US-guided PRP; however, they did not any use any SLBB as a diagnostic criterion [39].

The diagnostic criteria for defining pain of intra-articular SIJ origin are even less clear. Dreyfuss showed that SLBB improved PSIL pain but incompletely blocked nociceptive pain from the SIJ [7,50]. These findings verified anterior innervation. Theoretically, intra-articular anesthetic placed into the SIJ should interrupt the anterior nociceptive fibers. However, this assumption neglects the facts that the intra-articular space cannot be accessed reliably in every instance, that there is communication of the joint with the sacral neuroforamina in some patients, and that anterior SIJ capsular tears may exist that allow spread of injectate to extra-articular structures including nerve roots of the lumbosacral plexus [51,52]. Indeed, these issues limit the diagnostic accuracy of intra-articular SIJ injection. Furthermore, no clinical outcome studies have established a validated prognostic protocol to optimize the responder rate of SIJ-specific treatment. However, two reviews report a possible trend of better predictive value with dual SIJ blocks with a more significant improvement of pain as a predictor of successful therapeutic intervention [13,14]. A systematic review regarding SIJ blocks concluded that "it is not clear if image-guided intra-articular diagnostic injections with a local anesthetic predict a positive response to a therapeutic agent" [13].

The RCT published by Singla et al. diagnosed SIJ pain based on history and physical exam (three or more SIJ provocative tests), but without SIJ blocks. Results reveal that PRP into the SIJ was significantly more effective in pain reduction than steroids at three months. The pragmatic comparison of PRP to steroid is useful, as the effectiveness of IA SIJ steroid has been shown in a prior RCT [53]. Interestingly, patients in Maugers et al.'s RCT were also selected by history and physical exam and without diagnostic blocks [53]. Studies have shown that the presence of three or more positive SIJ maneuvers results in a positive likelihood ratio (LR) of 4.29 (95% CI = 2.34–8.58) [13,14]. Despite the significant LR, it is not clear if the SIJ maneuvers evoke pain within the SIJ, PSILs, or both.

Procedures should be accurate, precise, and safe. Diagnostic blocks should have target specificity to be valid. If an intended structure is anesthetized, a block is target-specific and valid. These principals assist providers in determining the pain generator(s). Interventions must be accompanied by appropriate image guidance. It is recommended that SIJC blocks be performed under fluoroscopy. Fluoroscopy with contrast shows needle location and helps the proceduralist avoid injection of medications into unintended structures (vasculature, etc.). Two studies included in this review utilized US as the procedural imaging technique [37,39]. Though US is an appealing option for logistical reasons, final needle location and injectate location are less certain. In a recent cadaveric study, US-guided needle placement in the SIJ was successful in 5% (95% CI = 0.9–23.6%) of the injections and 40% (95% CI = 21.9–61.3%) with fluoroscopy [52]. Navani et al. utilized fluoroscopy guidance for SIJ PRP delivery; however, there was no comment or visual evidence that contrast was used.

All of the published literature on this topic meeting the authors' criteria is positive. However, multiple levels of heterogeneity are present, not only regarding methodology and co-interventions but also with regards to the preparation and administration of the active agent, PRP. The variable published reported characteristics, established by the AAOS/NIH, are detailed in Table 1. The purpose of these established reporting standards was to aid progress with biologic research, to facilitate study reproducibility, and to identify therapeutic target agents and concentrations [40]. The highest quality study, by Singla et al., also had the highest percentage of reporting characteristics, with a total of 65% [37]. The other two studies reported 52% [38] and 39% [39] of the same reporting characteristic. If these reporting characteristics, including the composition of PRP injectate, are not reported, studies will lack the ability to be reproduced, and optimal concentration or dose effect, if any exists, cannot be known.

Quality of Evidence

The GRADE system was used to rate the overall quality of evidence. The evidence relating to improvement of pain and function with the treatment of PRP into either the SIJ or PSIJL was overall rated as very low quality. Per the GRADE system, all RCTs start as high quality, and observational studies without controls start as low quality. Per GRADE system recommendations, the RCT was upgraded for a significant measure of effect but downgraded to very low due to concerns of bias [41], imprecision [54], inconsistency [55], and indirectness [56]. The observational studies were downgraded from low to very low due to similar concerns. The final quality of evidence assessment of very low does not mean that the intervention is not effective, but rather, that the lack of evidence makes it difficult to draw any definitive conclusions from the results. The true effect may differ from what is reported in the current literature.

Strengths and Limitations

There are limitations to this review and the included studies. The strengths of this review are a specific research question, an in-depth literature search, and the

critical appraisal of all the studies meeting inclusion. Conversely, as a single author designed the search terms (DC) and two authors extracted the data (TB, JS), pertinent articles may have been overlooked, and errors in data extraction may have occurred.

The included studies had many limitations, including but not limited to the reasons defined by the GRADE system (discussed elsewhere), but also due to inconsistent reporting of demographics; patient diagnosis and selection; PRP preparation, storage, and administration; co-interventions, etc. (Table 2).

Future Research

Though the preliminary evidence for PRP in the treatment of SIJC pain is positive, it is very low quality. To accurately determine effectiveness, future researchers should address a number of areas in larger cohort studies and RCTs. First, a better diagnostic/prognostic protocol is needed to better identify true SIJC pain. Currently there is no validated protocol for diagnosing SIJC pain. Until there are validated selection criteria, providers should implement protocols that will reduce false positives. Limited evidence would suggest that the best diagnostic protocol for PSIL pain is $\geq$80% pain reduction after multisite, multi-depth dual SLBBs. The most specific diagnostic protocol for diagnosing intra-articular SIJ pain may be $\geq$80% pain reduction after dual SIJ blocks. Second, diagnostic targets and therapeutic procedures should be performed as accurately and safely as possible; currently, fluoroscopy is the most accurate and safe method of needle guidance. Efforts are needed to develop methods of potentially improving the accuracy of ultrasound-based needle guidance. Lastly, it is essential to understand the characteristics of the biologic agents used for treatment. We recommend implementing reporting characteristics, such as those of the AAOS/NIH, into future studies. Addressing and incorporating these topics into future research will allow an accurate assessment of the effectiveness of biologics for the treatment of SIJC pain.

Conclusions

The literature supporting the effectiveness of PRP for SIJC pain is very low quality according to the GRADE system. There is insufficient evidence to determine the effectiveness of PRP for SIJC pain. Well-designed RCTs and large cohort studies with consistent selection protocols and reporting characteristics are needed to determine the effectiveness of PRP and BMAC for the treatment of SIJC pain.

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