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NARRATIVE REVIEW

PM&R

Postprocedure protocols after intraarticular orthobiologic injections—A scoping review

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Abstract

Osteoarthritis is a chronic degenerative disease affecting 500 million people throughout the world. Although orthobiologics have been proposed as a symptom and disease modifying treatment for osteoarthritis, there is significant heterogeneity in the results of the orthobiologic procedures in the literature. One possible explanation for the heterogeneity is the inconsistent reporting and description of the postorthobiologic protocols. The goal of this scoping review was to identify the current literature on the use of orthobiologics for osteoarthritis and critically evaluate the postorthobiologic protocol within these studies. A total of 200 identified studies met inclusion criteria. In 37.5% of studies, there was no mention of a postorthobiologic protocol. Of the 125 studies that did mention a postorthobiologic protocol, only 38.4% included a rehabilitation protocol, 21.6% included postprocedure weightbearing restrictions, and only 2 (1.6%) mentioned the use of durable medical equipment. Nonsteroidal anti-inflammatory drug restriction was described in 91.2% of study protocols, whereas corticosteroids and immunosuppressants were restricted in 84.8% and 19.2% of protocols, respectively. The results of this scoping review demonstrate the inconsistent reporting of postorthobiologic procedure protocols in the literature, with significant heterogeneity in those that are described. These findings highlight the need for future research and improved reporting of postorthobiologic protocols.

INTRODUCTION

Osteoarthritis is a highly prevalent cause of pain and disability worldwide, affecting 500 million people globally.[1] Although conservative treatments including weight loss, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), bracing, and injections such as corticosteroid and hyaluronic acid have been used as a first-line treatment, they have been shown to provide meaningful long-term improvement in <50% of patients.[2] For those who do not find meaningful benefit from these treatment options, surgical intervention such as joint arthroplasty is often considered.

Orthobiologics such as platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and micro-fragmented adipose tissue (MFAT) offer an alternative treatment option for patients who do not achieve meaningful symptom improvement with standard conservative treatments. The majority of the current literature on orthobiologics for osteoarthritis involves the use of PRP, with a much lower number of studies evaluating BMAC and MFAT. For all three, there is significant heterogeneity in the reported outcomes. Many studies, both high and low level, have demonstrated that orthobiologics result in long-term symptom improvement, with some studies showing continued improvement at 5-year follow-up.[3–10] On the other hand, many studies have shown orthobiologics to be no better than placebo or corticosteroid.[11–13]

Various explanations for the variability of outcomes in the literature have been proposed, such as the importance of an adequate platelet "dose" being

delivered to the target region.[14] Another significant contributor to the variability of outcomes in the literature is the inconsistent reporting of the pre- and postorthobiologic protocol.[15,16] Townsend et al. demonstrated this inconsistent reporting of periprocedural protocols in studies on the use of PRP for the treatment of tendinopathy.[15,17] Factors such as the restriction of NSAIDs and other medications, activity limitations, and the timing and structure of formal postprocedure rehabilitation all are likely to affect outcomes after orthobiologic procedures. The lack of discussion of these postprocedure specifics makes interpretation of the data challenging and contributes to the heterogeneity of the literature.

The goal of our study was to perform a scoping review of the existing literature on the use of PRP, BMAC, and MFAT for the symptomatic treatment of osteoarthritis and systematically evaluate and describe the protocol specifics mentioned in those studies. Based on prior studies, we hypothesized that most studies would at least mention a postprocedure protocol, with significant heterogeneity in the reporting, type, and timing of those protocols.

METHODS

Search strategy

We performed a review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An electronic literature search of PubMed, EMBASE, and Web of Science on June 1, 2023 was performed. The full search terms are included in the supplemental file. The search strategy was developed with the assistance of a medical librarian. Titles and abstracts were screened for inclusion and relevance by a single author (K.R.). Any questions on inclusion were settled with a consensus of the study team. Data on aims, methodology, type of orthobiologic procedure, and postprocedure protocol specifics were extracted by two authors (K.R., T.F.). Any disagreements on data specifics were settled by a review with a third author (R.K.).

Inclusion and exclusion criteria

We included clinical studies investigating PRP, BMAC, and MFAT for the symptomatic treatment of osteoarthritis that were published in English from 2013 to June 2023. We excluded papers primarily investigating procedures using perinatal "stem cells," culture-expanded cells, stromal vascular fraction, prolotherapy, and ozone, as well as intraoperative or extraarticular injections. These papers were included only if PRP, BMAC, and/or MFAT were also included in the study. We also excluded nonclinical studies or trials that included <10 participants.

Data synthesis

Studies were first evaluated for whether there was mention of a postprocedure protocol. For studies in which a postprocedure protocol was identified, we extracted details related to[1] the restriction of oral NSAIDs and corticosteroids[2]; weight-bearing restrictions and use of durable medical equipment[3]; referral to formal physical therapy, including the timing and duration of physical therapy[4]; use of therapeutic modalities including cryotherapy, ultrasound, laser, and extracorporeal shockwave therapy[5]; restriction of periprocedural corticosteroid injections[6]; and restriction of oral immunosuppressants/immunotherapies.

RESULTS

The initial search resulted in 4077 articles. After deduplication, 3008 articles remained. Title and abstract review yielded 235 relevant articles. These articles then underwent a full-text review, and ultimately 200 articles were included based on inclusion and exclusion criteria (Figure 1). Out of the 200 articles, 125 (62.5%) discussed postprocedural protocols in some capacity (Table 1).

PRP was the only orthobiologic evaluated in 158 studies, BMAC was the only orthobiologic studied in 13 studies, and MFAT in 16 studies. Both PRP and BMAC were included in five studies, PRP and MFAT in five studies, BMAC and MFAT in two studies, and all three were included in one study. Of all studies

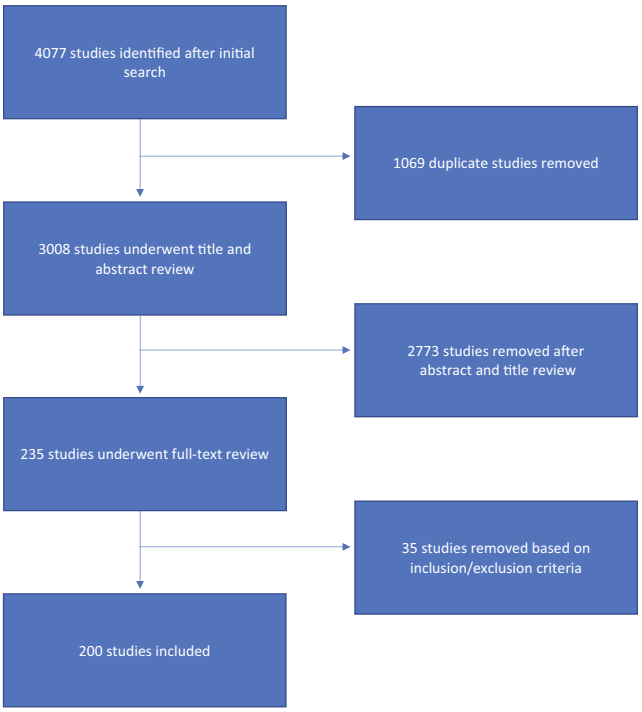

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for study selection.

TABLE 1 Characteristics of postorthobiologic protocols.

Postinjection rehabilitation	
Yes	48 (38.4%)
No	77 (61.6%)
NSAID restriction	
Yes	114 (91.2%)
No	11 (8.8%)
NSAID restriction preinjection	
Mean	9.5 days
Range	0–91 days
NSAID restriction postinjection	
Mean	163 days
Range	0–1095 days
Corticosteroid restriction	
Yes	106 (84.8%)
No	19 (15.2%)
Oral corticosteroid restriction preinjection	
Mean	109 days
Range	0–365 days
Oral corticosteroid restriction postinjection	
Mean	194 days
Range	0–365 days
Corticosteroid injection restriction preinjection	
Mean	12 days
Range	0–365 days
Corticosteroid injection restriction postinjection	
Mean	194 days
Range	0–365 days
Immunotherapeutic medication restriction	
Yes	24 (19.2%)
No	101 (80.8%)
Post-injection weightbearing restrictions	
Yes	27 (21.6%)
No	98 (78.4%)
Postinjection DME use	
Yes	2 (1.6%)
No	123 (98.4%)
Exercise restriction	
Yes	74 (59.2%)
No	51 (40.8%)

Abbreviations: DME, durable medical equipment; NSAID, nonsteroidal anti-inflammatory drug.

189 included the lower limb, with 176 (93.1%) of those studies including the knee joint.

Medication restrictions

The most commonly restricted medications were NSAIDs. 114 (91.2%) study protocols mentioned NSAID restriction either pre- or postprocedure. NSAIDs were restricted for a mean duration of 9.5 days before and 163 days after the procedure. Corticosteroids were restricted in 106 (84.8%) study protocols. The average duration of preprocedure restriction was 109 days for oral corticosteroids and 12 days for intraarticular corticosteroid injections into the target joint. Postprocedure, both oral and injectable corticosteroids were restricted for an average of 194 days. Eight articles excluded patients with any history of intraarticular corticosteroid injection and four articles excluded patients with any history of systemic corticosteroid use.

Oral and injectable immunotherapeutic medications were restricted in 24 (19.2%) protocols. Out these studies, the duration of restriction was variable, although 79.1% of studies restricted their use indefinitely postprocedure.

Postprocedure rehabilitation

A postprocedure rehabilitation program was included in 48 (38.4%) protocols. Of those, 13 included referral to formal physical therapy and 35 provided a home exercise program. On average, physical therapy was initiated 8 days postprocedure, and the average duration of physical therapy was 70 days (range 30–182 days). The specifics of the rehabilitation programs were highly heterogenous and varied significantly depending on the injected joint. Many programs focused on basic isometrics and range of motion exercises, whereas others included eccentric strengthening and progression to higher level functional movements.

Weightbearing restriction and durable medical equipment (DME)

Twenty-seven (21.6%) protocols, all involving the lower limb, included postprocedure weightbearing restrictions. One protocol involved a period of nonweightbearing for 48 hours, and 22 involved a period of partial weightbearing with the use of an assistive device. The degree of limb unloading was not specified. The remaining four protocols allowed patients to bear weight as tolerated. The duration of weightbearing restriction was <7 days in 59% of these protocols, >7 days in 22% of these protocols, and not specified in the remainder. Only two (1.6%) protocols described the use of postprocedure durable medical equipment, one requiring crutches and the other requiring a knee immobilizer.

Exercise limitation and return to activity

Exercise was limited in some capacity in 74 (59.2%) protocols; however, the degree of limitation was not

routinely described. Forty-five of these protocols limited exercise for <7 days, 10 protocols limited exercise between 7 and 14 days, and 8 articles limited exercise for >14 days. The longest period of restriction was 365 days postprocedure.

DISCUSSION

The most important finding in our paper is that 37.5% of studies on the use of orthobiologics for the symptomatic treatment of osteoarthritis did not describe a postprocedure protocol as part of the study design. Furthermore, there was significant heterogeneity within those in which protocols were described. The most commonly described aspect of postprocedure protocols was the restriction of periprocedural medications, in particular NSAIDs.

NSAIDs were restricted in some capacity in 91.2% of all protocols. The average duration of NSAID restriction prior to the procedure was 9.5 days, whereas the average duration of restriction postprocedure was 163 days. Although the ideal timing of restriction prior to an orthobiologic procedure is highly variable, most studies restricted for 7–14 days, likely based upon the half-life of most NSAIDs.[18] The large difference in the duration of restriction prior to and postprocedure is a result of many studies that restricted NSAIDs postprocedure for the entirety of their study period, which was predominantly 6–12 months. These findings suggest the currently studied postprocedure protocols reflect the desire to tightly control clinical trials as opposed to reflecting clinical practice. This further limits the ability to interpret the possible effectiveness of PRP in clinical settings that likely limit NSAIDs for much shorter periods of time.

The rationale for restricting NSAIDs prior to PRP is largely due to their antiplatelet effects, primarily through inhibition of the cyclooxygenase (COX) pathways.[19,20] There currently is no consensus regarding which NSAIDs should be withheld and which should not. A study by Kao et al. found that platelet aggregation was decreased in patients treated with nonselective NSAIDs and not those treated with COX-2 selective NSAIDs, concluding that the latter would not affect PRP and do not need to be withheld.[21] However, a narrative review by Madruger and Rodeo concluded that there is insufficient evidence in the literature to support the restriction of antiplatelet medications in patients who are receiving a PRP procedure.[22]

Oral and injectable corticosteroids were restricted in 84.6% of protocols. The average duration of restriction for injectable corticosteroids into the target joint preprocedure was significantly shorter than for oral steroids, on average 12 days versus 194 days, respectively. The cause of this large difference has previously been attributed to the longer acting and more robust systemic effects of oral steroids compared to intraarticular steroids, resulting in a more significant negative effect on the orthobiologic.

A postprocedure rehabilitation program was described in 38.4% of protocols, with only approximately one quarter of the rehabilitation programs including formal physical therapy. We found significant heterogeneity in both the formal physical therapy as well as home exercise program regimens. Prior studies have shown that rehabilitation is important to maximize outcomes in patients with osteoarthritis who have recently received an orthobiologic injection as well as in those who have not.[23–26] Early rehabilitation typically involves edema control and restoration of joint motion. Progression to strengthening of periarticular muscle groups is imperative to help stabilize and offload the joint.

Postprocedure joint protection in the form of weightbearing restrictions and DME was highly heterogenous and infrequently described. Although approximately half of all studies mentioned some form of activity or weightbearing postprocedure, only one study specified the degree of limitation as nonweightbearing for 48 hours, and the remaining studies did not provide specifics on the degree of limitation. Additionally, only two studies mentioned the use of DME.

Although the degree of joint unloading after an orthobiologic can be debated, it is known that both insufficient and excessive joint loading are detrimental to intraarticular tissue healing.[27–29] Ideal joint loading involves gradually progressive compressive loading, due to the biomechanical and physiologic composition of the osteochondral complex.[30,31] Although there is no consensus on the exact degree and rate of progression of joint loading, some studies have proposed general guidelines.[16,32] Future studies are needed to validate these guidelines.

The clinical importance of a postprocedure protocol as well as reporting of the protocol cannot be overstated.[33] The current literature on the use of orthobiologics for osteoarthritis is highly heterogenous, partly due to inconsistent reporting of the preparation and cellular composition of the orthobiologic, but equally as importantly due the inconsistent description of the postprocedure protocol. Replication of prior studies and interpretation of the data are not fully possible without consistent and uniform data reporting in the literature. Our findings highlight the inconsistent and inadequate reporting of postprocedure protocols which makes replication and interpretability of the orthobiologic literature challenging.

The strengths of our study include a structured literature review using well-established guidelines, as well as review of, and agreement on, protocol specifics among all authors. The main limitation is that we did not evaluate for any correlation between protocols and clinical outcomes. Future studies should investigate the

factors that are most important in postprocedure protocols in influencing outcomes.

CONCLUSION

The results of our review demonstrate that postprocedure protocols after orthobiologic injections for the symptomatic treatment of OA are not routinely described in the literature, and significant heterogeneity exists in those that are described. It is imperative that future studies on the use of orthobiologics include a description of the postprocedure protocol so that eventually there may be a more consistent consensus on the optimal protocols.

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DISCLOSURES

Ryan C. Kruse is a consultant for Lipogems SPO, LLC. His consulting role is not relevant to this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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