

Are Injections of Platelet-Rich Plasma Overused in Knee Osteoarthritis Despite Their Unproven Effectiveness?

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ABSTRACT

OBJECTIVE: To clarify whether intra-articular injections of platelet-rich plasma (PRP) are really effective for pain management in knee osteoarthritis.

METHODS: In this article, we have performed a narrative review of recent literature (2018-2019) to clarify whether intra-articular injections of PRP are truly effective.

RESULTS: A study with an evidence level of 1 that compared the long-term (5 years) clinical results of intra-articular injections of PRP versus hyaluronic acid (HA) in knee osteoarthritis showed that both treatments were effective in improving the knee's functional status. PRP did not provide superior clinical improvement over HA in terms of the duration of the effect or symptom-functional improvement at various points during the follow-up. The mean duration of the patient's subjective perception of pain relief was 9 months with HA and 12 months with PRP (no significant difference). Another trial with an evidence level of 1 compared the efficacy of intra-

articular injections of leukocyte-poor PRP, HA and normal saline solution (sham control group) in mild-moderate knee osteoarthritis. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and the International Knee Documentation Committee (IKDC) subjective score were obtained at the start of the study and at 1, 2, 6 and 12 months after treatment. The 3 groups showed statistically significant improvements in the outcome measures at 1 month; however, only the PRP group maintained significant improvement in both the WOMAC score and the IKDC score at 12 months.

CONCLUSIONS: Although promising initial results from the use of PRP have been published, most of the studies with an evidence level of 1 have had numerous problems, including small sample sizes, potentially inappropriate control cohorts and short follow-ups. Despite these limitations, there is still evidence to justify the use of PRP in treating knee osteoarthritis. However, further high-level human studies using standardized protocols are needed.

Key words: Knee; Osteoarthritis; Platelet-rich plasma (PRP); Intra-articular; Injections

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INTRODUCTION

Intra-articular injections of hyaluronic acid (HA) and corticosteroids (CS) have been employed for years to control pain in patients with painful knee osteoarthritis, with favorable but incomplete results (relative pain relief for weeks with CS and for 6-12 months with HA)^[1,2]. The purpose of the injections is to relieve pain for as long as possible to delay the need for surgery (total knee arthroplasty). In recent years, platelet-rich plasma (PRP) has been increasingly employed for treating knee pain in patients with osteoarthritis under the assumption that it was more effective in controlling pain than HA and CS.

The objectives of this narrative review of recent literature (2018-2019) are to determine the current status of the effectiveness of PRP

injections and whether they are overused without their effectiveness having been truly demonstrated.

METHODS

On July 15, 2019, we reviewed the recent literature (2018 and 2019) published in PubMed (MEDLINE) on the role of PRP in knee osteoarthritis using the keywords “PRP and knee”. We selected the articles with the highest level of evidence.

RESULTS

In September 2018, Piuze et al published a study that found that intra-articular injections of PRP were often employed for treating patients with knee osteoarthritis, although the clinical value and cost-effectiveness of these injections have not been definitely established^[3]. In other words, PRP injections appeared to be a potentially effective means of reducing pain and improving joint function in these patients, thereby enabling the patients to delay or avoid surgery. Using a 52-year-old simulated male patient with knee osteoarthritis, Piuze et al conducted a prospective cross-sectional study of 286 US centers using PRP injections. The authors contacted (by email or telephone) 179 centers (73.4% of all identified centers in the United States offering PRP injections for knee osteoarthritis), which reported a mean clinical efficacy of 76% and a mean reported price for a single PRP injection of \$714^[3].

In December 2018, Wasserman et al stated that PRP injections had been shown to be more beneficial than those with placebo and HA in knee osteoarthritis^[4]. However, the authors also stated that the effects of PRP on the knee should be further studied and that the type of PRP associated with the greatest possible benefit should be identified.

In December 2018, Cook and Smith published an article entitled “Why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee”^[5]. The authors stated that recent research on PRP injections in knee osteoarthritis had shown the injections’ efficacy and safety in all stages of the disease, although a trend towards better efficacy was observed when PRP was injected in the early stages of the disease.

In January 2019, Lin et al published a randomized controlled single-center trial with an evidence level of 1 that compared the efficacy of intra-articular injections of leukocyte-poor PRP, HA and normal saline solution (sham control group) in knee osteoarthritis^[6]. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and the International Knee Documentation Committee (IKDC) subjective score were obtained at the start of the study and at 1, 2, 6 and 12 months after treatment. The 3 groups showed statistically significant improvements in the outcome measures at 1 month; however, only the PRP group maintained significant improvement in both the WOMAC score and the IKDC score at 12 months. The authors’ conclusion was that intra-articular PRP injections can provide a clinically meaningful functional improvement for at least 1 year in patients with mild-moderate knee osteoarthritis.

In February 2019, Di Martino et al published a randomized controlled trial (with an evidence level of 1) that compared the long-term clinical results (5 years) of intra-articular injections of PRP versus HA in knee osteoarthritis^[7]. Their results showed that both treatments were effective in improving the functional status of the knee. PRP did not provide superior clinical improvement over HA in terms of the duration of the effect or symptom-functional improvement at various points of the follow-up. The mean duration of the patient’s subjective perception of pain relief was 9 months with HA and 12 months with

PRP (no significant difference). The only significant difference was observed in the reintervention rate at 24 months, which was significantly lower in the PRP group (22.6% vs. 37.1%)^[7].

In February 2019, Gato-Calvo et al published a narrative literature review^[8] that affirmed that, at present, the results of randomized controlled trials (RCTs) seemed to favor the use of PRP over other intra-articular treatments to improve pain scores in the short and medium term (6 to 12 months), although the general level of evidence was low. Therefore, the clinical effectiveness of PRP injections for treating knee osteoarthritis was still under debate, mainly due to the lack of standardization of PRP products, the scarcity of high-quality RCTs with a low risk of bias and the scarce stratification of patients for inclusion in the RCTs.

In March 2019, Huang et al published a prospective randomized controlled study to investigate whether the results of intra-articular PRP injections were superior to injections of HA and CS in patients with painful knee osteoarthritis^[9]. The study found no significant differences in WOMAC scores between the 3 groups at 3 months of treatment, although the PRP injections showed significantly lower (better) scores at 6, 9 and 12 months of treatment. Therefore, intra-articular PRP injections in the early stages of painful knee osteoarthritis appeared to be a valid therapeutic option. The clinical efficacy of PRP was comparable to that of HA and CS at 3 months. However, the efficacy of long-term PRP injections (6, 9 and 12 months) was superior to that of HA and CS^[9].

In March 2019, Han et al published a meta-analysis comparing PRP injections versus HA injections in patients with knee osteoarthritis^[10]. The authors observed that PRP injections reduced pain more effectively than HA injections at 6 and 12 months of follow-up. The authors also observed a better functional improvement in the PRP group based on the WOMAC scores at 3, 6 and 12 months. PRP and HA injections showed similar rates of adverse events. The authors’ main conclusion was that, in terms of pain relief and long-term functional improvement in knee osteoarthritis, PRP injections might be more effective than HA injections. However, the optimal PRP dose, time interval and frequency of injections, as well as the ideal treatment for the different stages of knee osteoarthritis, were still areas to be clarified in future investigations^[10].

In March 2019, Papalia et al evaluated the effects of combined intra-articular injections of PRP and hybrid HA on the clinical outcomes of patients with knee osteoarthritis^[11]. The authors divided the patients into 2 groups: group A (hybrid HA injections) and group B (injections of hybrid HA + PRP). Each patient was administered 3 injections in an interval of 1 week for 3 consecutive weeks. The authors concluded that the combined treatment of PRP and hybrid HA was not only a safe and effective procedure but was also significantly superior to isolated therapy with hybrid HA.

In April 2019, Simental-Mendía et al compared the clinical effectiveness of triple intra-articular PRP injection with that of a single injection in patients with mild knee osteoarthritis^[12]. The authors concluded that the triple PRP injection was clinically more effective at 48 weeks of follow-up than the single application.

In April 2019, Delanois et al published a systematic review and meta-analysis of the biologic therapies for treating knee osteoarthritis^[13]. The authors’ fundamental conclusion was that despite the promising initial published results of employing PRP, most studies with an evidence level of 1 had numerous problems, including small sample sizes, potentially inappropriate control cohorts and short follow-ups. Despite these limitations, the authors stated that there was still evidence to justify the use of PRP in treating knee osteoarthritis. However, they also mentioned that further high-level human studies

using standardized protocols were needed^[13].

In May 2019, O'Connell et al mentioned that more uniformly positive results were observed in several studies of intra-articular PRP injections in patients with knee osteoarthritis than when PRP was employed in other musculoskeletal tissues^[14]. However, both the methodological concerns and the satisfactory classification of PRP products impeded the proper characterization of this treatment. Therefore, further studies were needed to investigate the effect of platelet concentration and the inclusion of leukocytes on the therapeutic efficacy of PRP. There was also a need to determine the best timing, dosing, volume and frequency strategies. These issues need to be clarified before PRP injections, which appear to be a promising treatment, can be generalized for managing knee osteoarthritis^[14].

In May 2019, Burchard et al stated that the efficiency of PRP therapy in knee osteoarthritis did not depend on the level of cartilage damage^[15]. The study suggested that intra-articular PRP injections could improve pain relief in patients with painful knee osteoarthritis, regardless of the level of articular cartilage damage quantified by the Whole Organ Magnetic Resonance Imaging Score.

In June 2019, Cengiz et al stated that recent clinical studies indicate that the use of PRP could be beneficial for treating knee injuries^[16].

CONCLUSIONS

A study of US health centers using PRP injections reported a mean clinical efficacy of 76% and a mean price per PRP injection of \$714. PRP has been shown to be generally safe and free from significant adverse outcomes. The use of PRP has continuously increased, and a number of well-designed, double-blind, placebo-controlled clinical trials have been published. However, the clinical results of using PRP are multifactorial and depend on injury severity and the patient's characteristics. Although PRP is safe to use and can be easily applied in clinical practice, each patient should be individually considered to determine whether PRP could be beneficial. Further studies are needed to determine the effect of platelet concentration and the inclusion of leukocytes on the therapeutic efficacy of PRP. There is also a need to determine the best timing, dosing, volume and frequency strategies. The previously mentioned issues need to be clarified before PRP injections, which appear to be a promising treatment, can be generalized for managing knee osteoarthritis.

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