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Brief Commentary

The Role of Platelet Rich Plasma in the Treatment Algorithm of Knee Osteoarthritis

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Osteoarthritis (OA) is a progressive joint disease associated with both mechanical and biologic abnormalities of the articular cartilage and subchondral bone. In normal cartilage, a delicate balance exists between matrix synthesis and degradation; in OA, however, cartilage degradation exceeds synthesis. Treatment modalities include nonpharmacological, pharmacological, and surgical approaches. Intrarticular platelet rich plasma (PRP) has emerged as promising treatment for early stages of knee OA. PRP is an autologous blood product defined as a volume of plasma that has a supraphysiologic platelet count. PRP can accelerate the physiological recovery process, relieve pain, and contains anti-inflammatory and anti-bacterial activity. Although the mechanisms for these complex interactions are not completely understood, they are attributed to the more than 30 bioactive proteins contained in the alpha granules of platelets including growth factors and proteins, such as fibrin, fibronectin, vitronectin and thrombospondin. Several studies now have demonstrated that intra-articular PRP injections are safe and effective treatment to reduce pain and improve quality of life through increased function in knee osteoarthritis. The available literature suggests that PRP is a better option than hyaluronic acid for many knee OA patients. We identified eight comparative studies that demonstrated superiority of PRP as compared to HA for knee osteoarthritis. Considering what is known about the deleterious effects of local anesthetic and corticosteroids on soft tissue health, it may be time for a shift in the knee OA treatment algorithm to favor early intervention for regenerative therapies including platelet rich plasma.

Key words: Platelet rich plasma, hyaluronic acid, knee pain, knee osteoarthritis, arthritis, chondrotoxicity

Osteoarthritis (OA) is a progressive joint disease associated with both mechanical and biologic abnormalities of the articular cartilage and subchondral bone. In normal cartilage, a delicate balance exists between matrix synthesis and degradation; in OA, however, cartilage degradation exceeds synthesis. Although it may affect all joints, knee osteoarthritis is the most common type among adults, with a prevalence of 6% and a frequency reaching up to 40% with advancing age (1). Once articular cartilage is damaged, the healing potential is poor, subsequently leading to focal lesions of the cartilage and eventually OA.

Treatment modalities include non-pharmacological, pharmacological, and surgical approaches. Pharmacological approaches are often of limited benefit for OA pain; and serious side effects such as bleeding and gastrointestinal ulcers are associated with non-steroidal anti-inflammatory drugs. Non-pharmacological approaches including intraarticular corticosteroid and viscosupplementation have demonstrated success resulting in improvements in pain, function, and quality of life. Intraarticular platelet rich plasma (PRP) has emerged as a promising treatment for early stages of knee OA.

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PRP is an autologous blood product defined as a volume of plasma that has a supra-physiologic platelet count. These platelets contain numerous growth factors stored in alpha granules. Thus, increased platelet count is a secondary measurement of growth factor concentration, which can be delivered to damaged tissues to promote healing. The autologous nature of PRP provides for a reduced risk profile as compared to potential side-effects associated with the use of hyaluronic acid injection (HA). The risks associated with some HA preparations include acute pseudo-septic arthritis and granulomatous synovitis (2). Although the optimal protocol for PRP injection in knee OA is yet to be determined, the general conclusion drawn from current literature is that intra-articular knee PRP is safe and effective (3). The current treatment algorithm for knee OA includes the injection of corticosteroid and local anesthetics. However, numerous studies have shown that both local anesthetic and corticosteroids can have deleterious effects on soft tissues including chondrocytes (4-7). This effect may potentiate acceleration of OA and clinically correlates with the observed effect of diminishing efficacy of repeat intraarticular injections.

HA is the only currently FDA approved for treatment of knee OA. HA is a natural component of the connective tissue and cartilage. HA contributes to the viscoelastic capacity of the synovial fluid, acting as both a lubricant and shock absorber. Although HA may also play a role in regeneration of cartilage tissue, the mechanism of HA in the cartilage after administration is not known. It is believed that the anti-nociceptive properties of HA are related to creating a boundary layer around nociceptors and reducing hyperalgesic, spontaneous discharge in the arthritic joint (8-11).

PRP can accelerate the physiological recovery process, relieve pain, and contains anti-inflammatory and anti-bacterial activity (11-13). Although the mechanisms for these complex interactions are not completely understood, they are attributed to the more than 30 bioactive proteins contained in the alpha granules of platelets including growth factors and proteins, such as fibrin, fibronectin, vitronectin, and thrombospondin (14).

Current best evidence supports the effectiveness of PRP in the treatment of tendon injuries (15). More recently, a growing body of evidence has accumulated examining PRP as a treatment of knee OA. Several studies now have demonstrated that intraarticular PRP injections are a safe and effective treatment to reduce pain and improve quality of life through increased function (16-22).

Multiple authors have sought to compare the efficacy of PRP to HA for knee OA. The results of these studies suggest the non-inferiority or superiority of PRP as compared to HA for knee OA (Table 1).

Sanchez et al (16) published a retrospective cohort study in 2008 on their experience with PRP compared to HA in knee OA. These authors reported on 60 patients (2 groups of 30 patients) matched according to age, gender, body mass index, and radiographic severity utilizing the Western Ontario and McMaster Universities Arthritis Index (WOMAC) as the primary outcome measure. When compared with the HA control group, the PRP group demonstrated a higher treatment success rate with greater pain functional improvements ($P = 0.004$).

In 2011, Kon et al (17) published a multicenter 3-arm prospective comparative study of 150 patients with unilateral Kellgren-Lawrence grades 1 – 4 of knee OA. The outcomes of the study were measured with International Knee Documentation Committee (IKDC) and EuroQol visual analog scale (EQ-VAS) scores at 6 months. All 3 groups including the 2 HA groups showed improvement; however, the PRP group showed statistically greater and longer-term improvements in pain and function at 2 and 6 months follow-up ($P < 0.005$).

In 2012, Spakova et al (18) published results of a randomized, double-blind controlled study on 120 patients with unilateral Kellgren-Lawrence grades 1 – 3 knee OA. The outcomes of the study were measured with the WOMAC and the 11-point pain intensity numeric rating scale (NRS). One group received 3 intraarticular injections of PRP and the second group of patients received 3 injections of HA. Between the HA and PRP groups, the PRP group had statistically improved WOMAC and NRS scores at 3 and 6 months follow-up ($P < 0.01$).

In 2012, Sanchez et al (19) reported the first double-blinded, randomized controlled trial comparing the efficacy of PRP with HA in 176 patients with Ahlbäck grades 1 – 3 disease of the knee. The 176 patients

Table 1. Cohort studies and randomized controlled studies of platelet rich plasma injections for knee osteoarthritis.

Authors	Year published	Study design	Patients	Treatment arms	Outcome measures	Length of follow-up	Adverse effects to PRP group	Results
Sanchez et al (16)	2008	Retrospective cohort study	60 patients 60 joints	Group A (30 joints), 3x PRP q 1 week. Group B (30 joints), 3x HWHA q 1 week.	WOMAC	5 weeks	No severe adverse events were reported.	PRP group with better pain outcomes compared to HA group.
Kon et al (17)	2011	Prospective comparative study	150 patients 150 joints	Group A (50 joints), 3x PRP q 2 weeks. Group B (50 joints), 3x HWHA q 2 weeks. Group C (50 joints), 3x LWHA q 2 weeks.	EQ-VAS, IKDC	6 months	No severe adverse events were reported.	PRP more effective than HA in patients aged 50 years or younger at 6 months. In patients aged 50 years or younger, PRP and HA showed equal improvements.
Spakova et al (18)	2012	Randomized double blind controlled trial	120 patients 120 joints	Group A (60 joints), 3x PRP q 1 week. Group B (60 joints), 3x HWHA q 1week.	NRS, WOMAC	6 months	No severe adverse events were reported.	PRP group with greater improvement in pain and functional outcomes compared to HA group.
Sanchez et al (19)	2012	Randomized double blind controlled trial	176 patients 176 joints	Group A (89 joints) 3x PRP q 1 week. Group B (87 joints) 3x HWHA q 1 week.	Responders (50% pain reduction), WOMAC	6 months	No severe adverse events were reported.	PRP group had more responders (50% pain reduction) when compared to HA group.
Cerza et al (20)	2012	Randomized comparative trial	120 patients 120 joints	Group A (60 joints) 4x PRP q 1 week. Group B (60 joints) 4x HWHA q 1 week.	WOMAC	6 months	No severe adverse events were reported.	PRP group with a longer duration of improvements when compared to HA group.
Filardo et al (21)	2015	Randomized double blind controlled trial	183 patients 183 joints	Group A (94 joints) 3x PRP q 1 week. Group b (89 joints) 3x HWHA q 1 week.	EQ-VAS,IKDC, KOOS, Tegner	12 months	No severe adverse events were reported.	PRP and HA provided similar pain and functional outcomes.
Kilincoglu et al (22)	2015	Retrospective	118 patients 199 joints	PRP group 61 patients (102 knees) HA group 57 patients (97 knees) intra-articular PRP or HA treatments a total of 3 times, one week apart.	KSS, VAS	3, 6 months	No severe adverse events were reported.	Intraarticular PRP was more efficient than HA in the treatment of early knee osteoarthritis.

Table 1 cont. Cohort studies and randomized controlled studies of platelet rich plasma injections for knee osteoarthritis.

Authors	Year published	Study design	Patients	Treatment arms	Outcome measures	Length of follow-up	Adverse effects to PRP group	Results
Raeissadat et al (23)	2015	Randomized controlled trial	160 patients 160 joints	PRP group (n = 87) 2 intra-articular injections at 4-week interval. HA group (n = 73), 3 doses of intra-articular injection at 1-week interval.	WOMAC, SF-36	12 months	No severe adverse events were reported.	PRP group demonstrated superiority to the HA group (*P* , 0.001).
Lana et al (24)	2016	Multi-center, randomized controlled double blind prospective trial	105 patients with mild to moderate knee OA	HA (n=36), PRP (n=36), or HA+PRP (n=33).	WOMAC, VAS	1, 3, 6 and 12 months	No severe adverse events reported	PRP group with better pain outcomes compared to HA group at all intervals. HA + PRP superior to HA or PRP alone.
Paterson et al (25)	2016	Double-blind randomized controlled pilot	23 patients with knee OA	PA-PRP (n=12) HA (n=11)	VAS, KOOS, KQoL, maximum hopping distance, knee bends	4, 12 weeks	No severe adverse events reported	PA-PRP significantly improved VAS, KOOS Pain, KQoL Physical, and KQoL Emotional subscales at 4 and 12 weeks.
Montañez-Heredia et al (26)	2016	Double-blind randomized controlled clinical trial	53 patients with knee OA	Leukocyte poor PRP (n=27) HA (n=26)	VAS, KOOS scale, EUROQOL	3, 6 months	No severe adverse events reported	Both treatments improved pain in knee osteoarthritis patients without statistically significant differences between them. PRP injection was demonstrated to be more effective in lower osteoarthritis grades.
Cole et al (27)	2017	Randomized, prospective controlled trial	99 patients with knee OA	PRP (n=49) HA (n=50)	WOMAC pain subscale, IKDC, subjective knee evaluation, VAS for pain, Lysholm knee score	12, 24, 52 weeks	No severe adverse events reported	No difference between the groups in WOMAC pain score. PRP group demonstrated lower VAS scores at 24 and 52 weeks.

IKDC = International Knee Documentation Committee; EQ-VAS = EuroQol visual analog scale; KOOS = Knee Injury and Osteoarthritis Outcome Scores; PRP = platelet-rich plasma; WOMAC = Western Ontario and McMaster Universities Arthritis Index; NRS = Numeric Rating Scale; SF 36 = Short Form 36; KSS = Knee Society's Knee Scoring System

with symptomatic knee arthritis were randomized to receive injections of PRP or with HA. The primary outcome measure was a 50% decrease of knee pain from baseline to 6 months. Secondary outcomes were also measured using the WOMAC. Although not statistically significant, at 6 months the rate of response was 14.1 percentage points higher in the PRP group than in the HA group ($P = 0.44$). Furthermore, the rate of response defined as greater than 50% reduction in pain between the 2 groups showed opposite patterns, with a substantial improvement of the primary outcome in the PRP group at 24 weeks while the HA group revealed a gradual decline.

In 2012, Cerza et al (20) compared PRP with HA in 120 randomized patients with Kellgren-Lawrence grades 1 – 3 of knee OA. The 120 patients were randomized into a 1:1 ratio with one group receiving 4 intraarticular PRP injections and the other group 4 intraarticular HA injections. The outcomes were measured using the WOMAC before the injection and at one month, 3 months, and 6 months after the first injection. Compared to the HA group, the PRP had statistically better WOMAC scores at one month, 3 months, and 6 months follow-up ($P < 0.001$) (20). In addition, in patients with Kellgren-Lawrence grade 3 arthritis, treatment with HA was decidedly less effective than treatment with PRP.

Filardo et al (21) in 2015 published a randomized controlled trial of 192 patients comparing the benefit of PRP to HA. Patients underwent 3 weekly intraarticular injections of either PRP or HA. The outcomes of the study were measured using the International Knee Documentation Committee (IKDC) subjective score, as well as the Knee Injury and Osteoarthritis Outcome Score (KOOS), EQ-VAS, and Tegner score. Both treatments proved to be effective in reducing symptoms and improving functional status. The IKDC score in the PRP group rose from 52.4 ± 14.1 to 66.2 ±16.7 at 12 months ($P < 0.0005$). On the other hand, the IKDC score of the HA group rose from 49.6 ± 13.0 to 64.2 ± 18.0 at 12 months ($P < 0.0005$). In addition, in the HA group, 2 patients reported severe pain and swelling while the PRP group had no major adverse events.

Kilincoglu et al (22) in 2015 reported results of 118 patients with Kellgren-Lawrence stage 1 and 2 of knee OA in a retrospective study comparing PRP and HA (22). The patients received intraarticular injections of PRP or HA for a total of 3 treatments, one week apart. The patients were evaluated using the Knee Society's Knee Scoring System (KSS) and the VAS scoring system before the treatment and at 3 and 6 months after the treatment. At 3 months and 6 months post treatment, the PRP group had significantly improved KSS ($P < 0.001$) and VAS ($P < 0.001$).

Also in 2015, Raeissdat et al (23) published a randomized controlled trial comparing the efficacy of PRP with HA in 180 patients with grade 1 – 4 Kellgren-Lawrence scale of knee OA. In the PRP group, 2 intraarticular injections at 4-week intervals were performed, and in the HA group, 3 doses of intraarticular injection at one-week intervals were performed. All patients were evaluated prior to treatment and at 12 months using the WOMAC and Short Form (SF)-36 questionnaires. At 12 month follow-up, both groups had improved WOMAC pain scores and bodily pain; however, the PRP group had better results compared to the HA group ($P < 0.001$).

Lana et al (24) published the results of a 2016 multi-center, randomized, controlled, double blind, prospective trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. the study randomly allocated105 patients with mild to moderate knee OA to HA (n = 36), PRP (n = 36), or HA+PRP (n = 33). Each patient received 3 intra-articular knee injections of their assigned substance, at 2 week intervals. Clinical outcomes were evaluated using the WOMAC and VAS questionnaire at baseline and after 1, 3, 6 and 12 months. The PRP group demonstrated significant reduction in VAS scores at all follow up intervals when compared to HA. Combining HA and PRP resulted in a significant decreases in pain ($P = 0.0001$) and functional limitation ($P = 0.0001$) when compared to HA alone at 1 year post treatment; and significantly increased physical function at 1 ($P = 0.0004$) and 3 ($P = .011$) months when compared to PRP alone.

In 2016, Paterson et al (25) published the results of a double-blind randomized controlled pilot comparing photo-activated PRP (PA-PRP) to HA in people with knee OA. Twelve subjects were randomized to the PA-PRP group and 11 to the HA group. Outcomes included recruitment and safety data, VAS, the

KOOS, KQoL scale, and maximum hopping distance and number of knee bends in 30 seconds, at 4 and 12 weeks. two participants from the PA-PRP group reported minor pain and swelling from the injections. The PA-PRP group demonstrated significant improvements in the VAS ($P < 0.01$, ETA = 0.686), KOOS Pain ($P < 0.05$, ETA = 0.624), KQoL Physical ($P < 0.05$, ETA = 0.706) and KQoL Emotional subscales ($P < 0.05$, ETA = 0.715) at 4 and 12 weeks. The PA-PRP group also significantly improved hoping ($P < 0.05$, ETA=0.799) and knee bends ($P < 0.01$, ETA=0.756) at 4 or 12 weeks. The HA group showed improvements on only the KOOS Function subscale at 12 weeks ($P < 0.01$, ETA = 0.602). After controlling for baseline values, there were no significant between-group differences at either time-point.

Also in 2016, Montañez-Heredia et al (26) published the results of a double-blind randomized controlled clinical trial to evaluate the efficacy of injecting autologous PRP versus HA in knee OA. There were 27 patients randomized to PRP and 26 patients randomized to HA completed the trial. PRP group patients were injected with PRP rich in platelets and weak in leukocytes and red blood cells. Pain and functional improvements were assessed pre- and post-treatment at, 3 and 6 months follow-up using VAS; the KOOS scale and the EUROQOL. Adverse events in both groups did not show significant differences. There was pain related to infiltration in nine of 27 PRP injections and in 4 of 26 for HA. Both groups presented pain reduction at 6 months. The VAS scores for the PRP group improved by at least 50% from their initial value, particularly at 3 months following the final infiltration, with results resembling those of the HA group at 6 months. PRP was more effective in patients with lower osteoarthritis grades. Both treatments improved pain in knee osteoarthritis patients without statistically significant differences between them. PRP injection was demonstrated to be more effective in lower osteoarthritis grades.

In 2017 Cole et al (27) published the results of a randomized controlled trial comparing hyaluronic acid and platelet-rich plasma injection for knee OA. 49 patients were randomized to treatment with PRP and 50 randomized to treatment with HA. Clinical data were collected before treatment and at 4 time points up to 52 weeks. Outcome measures were WOMAC pain subscale, IKDC, subjective knee evaluation, VAS for pain, Lysholm knee score, and difference in intra-articular biochemical marker concentrations. No difference was seen between the groups in WOMAC pain score. There were significantly higher IKDC score in the PRP group compared with the HA group at 24 weeks ($P = .013$) and at final follow-up (52 weeks) ($P = .003$). The PRP group demonstrated lower VAS scores at 24 ($P = .0096$) and 52 weeks ($P = .0039$).

Since PRP is obtained from the patients' own blood, immune reaction or blood-borne diseases are highly unlikely to occur. No serious side effects or complications were demonstrated regarding administration of PRP in any of the studies. Considering what is known about the deleterious effects of local anesthetic and corticosteroids on soft tissue health, it may be time for a shift in the knee OA treatment algorithm to favor early intervention for regenerative therapies including platelet rich plasma with or without hyaluronic acid.

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