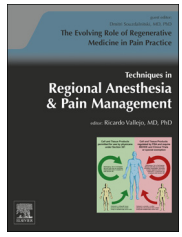
Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/trap



Platelet-rich plasma injections for knee osteoarthritis: Systematic review of duration of clinical benefit

Dmitri Souzdalnitski, MD, PhD[a,*], *Samer N. Narouze, MD, PhD, FIPP*[a], *Imanuel R. Lerman, MD, MS*[b], *Aaron Calodney, MD*[c]

[a]*Center for Pain Medicine, Western Reserve Hospital, Cuyahoga Falls, Ohio*
[b]*Department of Anesthesiology, University of California, San Diego, La Jolla, California*
[c]*Texas Spine & Joint Hospital, Tyler, Texas*

ARTICLE INFO

Keywords:
Platelet-rich plasma
Injections
Knee
Osteoarthritis
Regenerative medicine

ABSTRACT

Both researchers and clinicians have exhibited growing interest in the use of platelet-rich plasma (PRP) and other autologous products for a variety of clinical conditions. Newly published data suggest that PRP injections can be an effective complement to conventional management strategies for knee osteoarthritis (OA) and chondropathy. Using a systematic review approach, we sought to synthesize the published data on the duration of clinical effect of PRP on knee OA and chondropathy. We systematically searched PubMed for all reports published in any language between the earliest available date and July (fourth week) of 2015 using the following key words: platelet, rich, plasma, knee, and osteoarthritis. If double-blind randomized, controlled trials were not available, we included other clinical trials and observational studies. We further searched for the association of the same keywords (platelet, rich, plasma, knee) and chondropathy. After reviewing abstracts, we acquired full-text papers where appropriate. We categorized the level of evidence for the duration of treatment efficacy according to Guyatt and coauthors. Twenty-four relevant studies encompassing 2,385 patients were included in the review. Studies reported clinical outcomes from intra-articular injection of PRP or recounted autologous products. The results showed a consistent improvement in patient pain scores and functional indexes for 6 months after initiation of injections. The residual clinical effect was typically observed beyond 6 months of follow-up in most of the studies. Pain and functional scores decreased after 12 months of follow-up but remained higher than the base scores in the majority of studies. Some suggested that annual injections improved treatment outcomes after 18 months of follow-up. Data from available clinical reports suggest that the PRP administration results in decreased pain and enhanced functional status. The duration of beneficial clinical effects after administration of PRP or recounted autologous products for patients with knee OA and chondropathy was stable up to 6 months following completion of regenerative therapy. The pain and functional scores worsened after 12 months of follow-up but were still better than pre-injection scores according to the majority of publications. The analysis is limited by the wide variability of available studies.

*Corresponding author.
E-mail address: ds241014@ohio.edu (D. Souzdalnitski).

http://dx.doi.org/10.1053/j.trap.2016.09.012
1084-208X/

Introduction

Knee cartilage counteracts pressure to bony parts of the joint when exposed to compressive and shearing forces that are inevitably present with movement in the knee joint.[1] Radiography, magnetic resonance imaging, ultrasonography, arthroscopy, and other diagnostic modalities can detect degenerative changes in cartilage (chondropathy).[2] Degenerative changes in cartilage, synovia, and bony elements of the knee joint are typically asymptomatic in early stages.[3] Progression of chondropathy and underlying bone pathology, commonly secondary to aging, overuse, or trauma, usually results in symptomatic knee osteoarthritis (OA).

Knee OA is a disease of the entire joint, not just cartilage, that involves synovia, menisci, ligaments, and subchondral bone.[2] The exact causes are not completely identified, but are believed to be a consequence of biomechanical forces, metabolic disarrays, overuse, or trauma.[1] The pain and joint stiffness experienced by patients result from damage to these tissues. Disease onset is gradual. Progression of knee OA is associated with a worsening structural and metabolic environment in the knee joint, accompanied by knee pain, joint effusion, and local hyperthermia in advanced cases.

Eventually, knee OA becomes a disease of the entire body because progressive degeneration in the knee joint negatively affects physical performance and creates limitations in routine activities. These changes, in turn, may trigger a chronic pain disorder. The chronic pain is typically much more than a painful sensation; it is accompanied by anxiety, depression, occupational and social problems, dependence on medications, and potential adverse effects of treatment. There is currently no cure for OA.[1]

Knee OA typically is discovered in middle age and affects 50% of the population aged 65 years and older. According to a report from the centers for disease control and prevention, the prevalence of symptomatic OA is as high as 16.7% in all individuals older than 45 years.[1] It is 1 of the 5 top causes of disability.[4] Estimated hospital expenditures of total knee joint replacements are $28.5 billion in the United States.[1] The direct health care costs likely represent only a small portion of the economic effect of OA. Estimating the overall economic effect of knee OA on workforce efficiency, absenteeism, and necessary help within households as well as the effect of decreased physical activity on cardiovascular, endocrine, and other organ systems is difficult.[5] Published causes of death secondary to knee OA do not include, for example, the number of people who die of the complications of nonsteroidal anti-inflammatory drugs used for the knee OA.[2]

Management of knee OA remains less than satisfactory, despite the use of comprehensive treatment that includes physical rehabilitation, manipulation, and oral and parenteral drugs. Benefits of arthroscopic surgery are unclear, and, even if present, last less than 2 years.[6] The definitive treatment remains knee replacement, which is not without adverse effects and limitations.[7]

Intra-articular knee injections have been used for the treatment of knee arthritis for more than a century. The first available report of intra-articular knee injection was published in 1897, approximately 3 centuries after initial experiments on injections in humans and approximately 40 years after invention of the hollow needle.[8] Corticosteroids and hyaluronic acid are the most commonly injected agents for knee OA.[9] Despite their widespread use, corticosteroid injections appear to be predominantly appropriate for knee OA with synovitis. Their clinical effect is typically only a few weeks, according to most studies,[9] and, according to some reports, up to 24 weeks.[10]

Viscosupplementation has been considered a safe and efficacious treatment for symptomatic knee OA. Effects characteristically are sustained up to 6 months after injection, according to most of the systematic reviews, including a recent evidence-based summary of high-quality, placebo (normal saline)-controlled trials.[11] Viscosupplementation has insignificant and clinically inapt benefit and unfavorable side effects according to other systematic reviews.[12] Dissatisfaction with treatment outcomes for knee OA has prompted an intensive search for alternative injectable treatment agents that can intensify the restorative reactions in synovia, cartilage, bone, meniscal tissue, ligaments, and knee joint tissues affected by injury or degeneration.[13]

Platelet-rich plasma (PRP) and recount autologous products (eg, platelet lysates, conditioned serum, selected growth factors, and peripheral blood stem cells) have garnered attention because they use the patient's own cells and PRP growth factors are contained in platelet alpha-granules. Agents prepared from a patient's own cells are believed to provide an environment that may be beneficial to reparative processes because of supraphysiologic concentrations of these products.[14] Intra-articular use of autologous biologic products applied directly to the synovia, cartilage, bone, meniscal tissue, or ligament is expected to stimulate a natural regenerative process.[15] Experimental studies propose that PRP injections may foster regeneration of the entire joint environment, including, but not limited to, cartilage, bone, and synovia.[15-19] Newly published data suggest that PRP injections can effectively complement conventional management strategies of knee OA and chondropathy.[13-15,20-31] However, the duration of clinically meaningful benefits remains unclear.

Objectives

We used a systematic review methodology to analyze available clinical studies reporting on the duration of clinical effects of PRP in patients with knee OA and knee chondropathy.

Methods

We systematically searched PubMed for all reports published in any language between the earliest available date and July (fourth week) of 2015 using the following keywords: platelet, rich, plasma, knee, and osteoarthritis. The following is an example of the primary query performed for the PubMed database: ("platelet-rich plasma"[MeSH Terms] OR ("platelet-rich"[All Fields] AND "plasma"[All Fields]) OR "platelet-rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]) AND ("osteoarthritis, knee"[MeSH Terms] OR ("osteoarthritis"[All Fields] AND "knee"[All Fields]) OR "knee

osteoarthritis"[All Fields] OR ("knee"[All Fields] AND "osteoarthritis"[All Fields]). We searched primarily for randomized, controlled trials (RCTs). If double-blind RCTs were not available, we included retrospective studies and other clinical trials. We furthermore extended the search for the association of the same keywords (platelet, rich, plasma, and knee) and chondropathy using the secondary query: ("platelet-rich plasma"[MeSH Terms] OR ("platelet-rich"[All Fields] AND "plasma"[All Fields]) OR "platelet-rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]) AND ("knee"[MeSH Terms]) OR ("knee"[All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields]) AND ("cartilage diseases"[MeSH Terms] OR ("cartilage"[All Fields] AND "diseases"[All Fields]) OR "cartilage diseases"[All Fields] OR "chondropathy"[All Fields]).

After reviewing abstracts, we acquired full-text articles wherever appropriate. We categorized the level of evidence for the duration of treatment efficacy according to Guyatt et al[32] (Table 1). This approach to classifying the evidence considers the study type and quality. Moreover, 2 of the authors (D.S. and I.L.) independently performed the search and extracted data from articles, with disagreements resolved by the other 2 authors (S.N. and A.C.).

Search results

The primary query yielded 117 records. The secondary query yielded 23 records. The collected literature focused on PRP and recounted autologous products for treatment of knee OA and chondropathy. A total of 24 relevant studies encompassing 2315 patients were included in the analysis (Figure; Table 2). The analysis focused on the duration of treatment effects of PRP or recounted autologous products injections for knee OA. Although the outcome measurements in these studies varied significantly, all were assessed using conventional pain and function scales. The volume of blood used for PRP preparations, methods of PRP preparations, presence of white blood cells and other cell types, type of anticoagulant, number and timing of knee injections, and other functions varied significantly between studies.

Discussion

The perpetual quest for injectable agents for management of pain and dysfunction associated with knee OA has

Table 1 – Levels of evidence and recommendations.

Grade of recommendation or description	Benefits vs risk and burdens	Methodological quality of supporting evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly overweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate-quality evidence	Benefits clearly overweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low, or very low-quality evidence	Benefits clearly overweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when stronger evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risk and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risk and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates, benefits, risk and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

Adapted from Guyatt et al.[32]

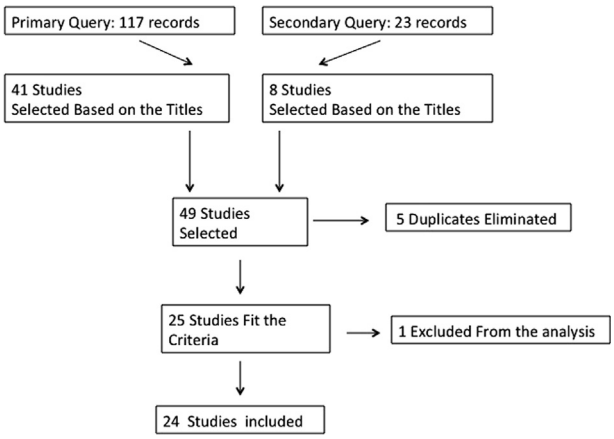


Fig – PRIZMA flow diagram.

resulted in an array of novel regenerative medicine choices: PRP, platelet lysates, conditioned serum, selected growth factors, peripheral blood stem cells, and others assumed to provide a plausible environment for reparative processes in the degenerating or injured knee joint.[14] The straightforward reasonability of this concept, strong support from experimental studies, wide use in sports medicine, and relative ease of preparation of an injectate has increased the popularity of PRP use in the management of knee OA.[21]

Initial clinical studies published in 2010 demonstrated that PRP might be a feasible management option for the pain and functional disability accompanying knee OA.[33,34] The number of publications has grown significantly since then.[35] Pain, function, and quality of life for patients with knee OA treated with PRP were assessed in a number of reviews. Studies and reviews of the clinical evidence suggest that PRP could be a feasible treatment option for temporarily alleviating pain and improving function as well as improving quality of life. However, the duration of effects of PRP and recounted autologous products either has not been assessed systematically or was not included in all of the available publications.[13-15,20-31]

Our investigation systematically explored the duration of effects of PRP and recounted autologous products (Table 2). The results showed a consistent and clinically significant improvement in pain scores and functional indexes for at least 6 months in all included studies.[33-56] Moreover 2 studies that involved further assessment of mid-term outcomes reported a sustained effect at 8.6 and 9 months, respectively, after initiation of injection therapy.[39,48] Nine of the studies reported decreased therapeutic effect at 6 months from the start of injection therapy, but in most of the studies, the pain and functional status scores did not fall below baseline scores acquired before the first injection.[34-36,38,40,41,43,44,47,51] Authors of one of the recent RCTs stated that the outcomes were furthermore improved at 18 months by annual repetition of the PRP treatment.[44]

Table 2 – The duration of clinical effect of platelet-rich plasma and related autologous preparations for patients with knee osteoarthritis and knee chondropathy.

	Source	Type of study	Level of evidence	Sample size	Duration of clinical effect
1.	Al-Ajlouni et al[36]	Prospective open-label study	2A	$n = 160$	12 mo
2.	Cerza et al[37]	RCT	1A	$n = 120$	6 mo
3.	Filardo et al[38]	RCT	1A	$n = 192$	12 mo
4.	Filardo et al[39]	Prospective observational study	1B	$n = 90$	9 mo
5.	Filardo et al[40]	RCT	1B	$n = 109$	12 mo
6.	Filardo et al[41]	RCT	1B	$n = 144$	12 mo
7.	Forogh et al[42]	RCT	1B	$n = 44$	6 mo
8.	Gobbi et al[43]	Observational study	1C	$n = 50$	12 mo
9.	Gobbi et al[44]	RCT	1B	$n = 93$	12 mo
10.	Gormeli et al[45]	RCT	1A	$n = 162$	6 mo
11.	Guler et al[46]	Observational study	1C	$n = 132$	6 mo
12.	Hart et al[47]	Observational study	1C	$n = 50$	12 mo
13.	Jang et al[48]	Prospective observational study	1C	$n = 65$	8.8 mo
14.	Kon et al[33]	Prospective observational study	1C	$n = 100$	6 mo, worse at 12 mo, but not back to the basal level
15.	Kon et al[49]	Prospective comparative study	1B	$n = 150$	6 mo
16.	Li et al[50]	RCT	1B	$n = 30$	6 mo
17.	Mangone et al[51]	Observational study	1C	$n = 72$	6 mo, worse at 12 mo, but not back to the basal level
18.	Patel et al[52]	RCT	1A	$n = 78$	6 mo
19.	Raeissadat et al[53]	Observational study	1C	$n = 60$	6 mo
20.	Raeissadat et al[35]	RCT	1B	$n = 160$	12 mo
21.	Sampson et al[34]	Prospective observational study	1C	$n = 14$	12 mo
22.	Say et al[54]	Observational prospective	1B	$n = 90$	6 mo
23.	Spakova et al[55]	Prospective observational study with control group	1B	$n = 120$	6 mo
24.	Torrero et al[56]	Observational study	1C	$N = 30$	6 mo

Our analysis is limited by the wide variability of the available studies. Overall, the variability in the duration of therapeutic effects is related to variability in study design. Other variables possibly affecting the duration of clinical effects are related to specific autologous product preparations (eg, volume of blood used for PRP preparations, methods of PRP preparation, white blood cells count in the injectate, and type of anticoagulant used) and treatment techniques (number and timing of knee injections, patient use of nonsteroidal anti-inflammatory drugs, frequent use of opioids in the United States compared with other countries, and use of physical therapy and other treatment modalities). The duration of clinical effects depends on patient characteristics as well. These include age, sex, body mass index, presence of clinical depression, and worker compensation status and were not consistently reported in the studies.

Author conclusions

The data from available clinical reports suggest that the duration of beneficial clinical effects of PRP or recounted autologous products injection (decreased pain and enhanced functional status) for patients with knee OA and chondropathy remained stable from the end of the regenerative therapy up to 6 months of follow-up. Pain and functional scores worsened after 12 months of follow-up, but they were still better than preinjection scores in most publications. The analysis is limited by the wide variability of available studies.

REFERENCES

1. *Osteoarthritis*. Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion; May 16, 2014. Assessed July 31, 2015.
2. Brody LT. Knee osteoarthritis: clinical connections to articular cartilage structure and function. *Phys Ther Sport*. 2014;16(4):301–316.
3. Stoppiello LA, Mapp PI, Wilson D, Hill R, Scammell BE, Walsh DA. Structural associations of symptomatic knee osteoarthritis. *Arthritis Rheumatol*. 2014;66(11):3018–3027.
4. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheumatol*. 2008;59(9):1207–1213.
5. Losina E, Burbine SA, Suter LG, Hunter DJ, Solomon DH, Daigle ME, et al. Pharmacologic regimens for knee osteoarthritis prevention: can they be cost-effective? *Osteoarthritis Cartilage*. 2014;22(3):415–430.
6. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *Br Med J*. 2015;350:h2747.
7. Beswick AD, Wylde V, Gooberman-Hill R. Interventions for the prediction and management of chronic postsurgical pain after total knee replacement: systematic review of randomised controlled trials. *BMJ Open*. 2015;5(5):e007387.
8. Holwell EB. Two cases of tuberculous disease of the knee-joint treated by iodoform injections: recovery. *Br Med J*. 1897;2(1911):397–398.
9. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. *Pain Med*. 2012;13(6):740–753.
10. Lomonte AB, de Morais MG, de Carvalho LO, Zerbini CA. Efficacy of triamcinolone hexacetonide versus methylprednisolone acetate intraarticular injections in knee osteoarthritis: a randomized, double-blinded, 24-week study. *J Rheumatol*. 2015;42(9):1677–1684.
11. Strand V, McIntyre LF, Beach WR, Miller LE, Block JE. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. *J Pain Res*. 2015;8:217–228.
12. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180–191.
13. LaPrade CM, James EW, LaPrade RF, Engebretsen L. How should we evaluate outcomes for use of biologics in the knee? *J Knee Surg*. 2015;28(1):35–44.
14. Mascarenhas R, Saltzman BM, Fortier LA, Cole BJ. Role of platelet-rich plasma in articular cartilage injury and disease. *J Knee Surg*. 2015;28(1):3–10.
15. Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(9):2459–2474.
16. Sakata R, McNary SM, Miyatake K, et al. Stimulation of the superficial zone protein and lubrication in the articular cartilage by human platelet-rich plasma. *Am J Sports Med*. 2015;43(6):1467–1473.
17. Osterman C, McCarthy MB, Cote MP, et al. Platelet-rich plasma increases anti-inflammatory markers in a human coculture model for osteoarthritis. *Am J Sports Med*. 2015;43(6):1474–1484.
18. Almasry SM, Soliman HM, El-Tarhouny SA, Algaidi SA, Ragab EM. Platelet rich plasma enhances the immunohistochemical expression of platelet derived growth factor and vascular endothelial growth factor in the synovium of the meniscectomized rat models of osteoarthritis. *Ann Anat*. 2015;197:38–49.
19. Liu J, Song W, Yuan T, Xu Z, Jia W, Zhang C. A comparison between platelet-rich plasma (PRP) and hyaluronate acid on the healing of cartilage defects. *PLoS one*. 2014;9(5):e97293.
20. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49(10):657–672.
21. Lai LP, Stitik TP, Foye PM, Georgy JS, Patibanda V, Chen B. Use of platelet-rich plasma in intra-articular knee injections for osteoarthritis: a systematic review. *PM R*. 2015;7(6):637–648.
22. Tietze DC, Geissler K, Borchers J. The effects of platelet-rich plasma in the treatment of large-joint osteoarthritis: a systematic review. *Phys Sportsmed*. 2014;42(2):27–37.
23. Pourcho AM, Smith J, Wisniewski SJ, Sellon JL. Intraarticular platelet-rich plasma injection in the treatment of knee osteoarthritis: review and recommendations. *Am J Phys Med Rehabil*. 2014;93(11 suppl 3):S108–S121.
24. Dold AP, Zywiel MG, Taylor DW, Dwyer T, Theodoropoulos J. Platelet-rich plasma in the management of articular cartilage pathology: a systematic review. *Clin J Sport Med*. 2014;24(1):31–43.
25. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2014;95(3):562–575.
26. Andia I, Abate M. Knee osteoarthritis: hyaluronic acid, platelet-rich plasma or both in association? *Expert Opin Biol Ther*. 2014;14(5):635–649.
27. Smelter E, Hochberg MC. New treatments for osteoarthritis. *Curr Opin Rheumatol*. 2013;25(3):310–316.

28. Rodriguez-Merchan EC. Intra-articular injections of hyaluronic acid and other drugs in the knee joint. hss journal: the musculoskeletal journal of hospital for special. *Surgery*. 2013; 9(2):180–182.
29. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. *Arthroscopy*. 2013;29(12):2037–2048.
30. Hsu WK, Mishra A, Rodeo SR, et al. Platelet-rich plasma in orthopaedic applications: evidence-based recommendations for treatment. *J Am Acad Orthop Surg*. 2013;21(12):739–748.
31. De La Mata J. Platelet rich plasma. A new treatment tool for the rheumatologist? *Reumatol Clin*. 2013;9(3):166–171.
32. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest*. 2006;129(1):174–181.
33. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):472–479.
34. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil*. 2010;89(12):961–969.
35. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet- rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *ClinMed Insights Arthritis Musculoskelet Disord*. 2015;8:1–8.
36. Al-Ajlouni J, Awidi A, Samara O, et al. Safety and efficacy of autologous intra-articular platelet lysates in early and intermediate knee osteoarthrosis in humans: a prospective open-label study. *Clin J Sport Med*. 2015;25(6):524–528.
37. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med*. 2012;40(12):2822–2827.
38. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575–1582.
39. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(4):528–535.
40. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord*. 2012;13:229.
41. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(10):2082–2091.
42. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. *J Sports Med Phys Fitness*. 2016;56(7-8): 901–908.
43. Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. *Sports Health*. 2012;4(2):162–172.
44. Gobbi A, Lad D, Karnatzikos G. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(8):2170–2177.
45. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2015 [Epub ahead of print].
46. Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. *Eur J Orthop Surg Traumatol*. 2015; 25(3):509–513.
47. Hart R, Safi A, Komzak M, Jajtner P, Puskeiler M, Hartova P. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. *Arch Orthop Trauma Surg*. 2013;133(9):1295–1301.
48. Jang SJ, Kim JD, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur J Orthop Surg Traumatol*. 2013;23(5):573–580.
49. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy*. 2011;27(11): 1490–1501.
50. Li M, Zhang C, Ai Z, Yuan T, Feng Y, Jia W. Therapeutic effectiveness of intra-knee-articular injection of platelet-rich plasma on knee articular cartilage degeneration. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2011;25(10):1192–1196.
51. Mangone G, Orioli A, Pinna A, Pasquetti P. Infiltrative treatment with platelet rich plasma (PRP) in gonarthrosis. *Clin Cases Miner Bone Metab*. 2014;11(1):67–72.
52. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(2):356–364.
53. Raeissadat SA, Rayegani SM, Babaee M, Ghorbani E. The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. *Pain Res Treat*. 2013;2013: 165967.
54. Say F, Gurler D, Yener K, Bulbul M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech*. 2013;80(4):278–283.
55. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil*. 2012;91(5):411–417.
56. Torrero JI, Aroles F, Ferrer D. Treatment of knee chondropathy with platelet rich plasma. Preliminary results at 6 months of follow-up with only one injection. *J Biol Regul Homeost Agents*. 2012;26(2 suppl 1):71S–78SS.