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Platelet-Rich Plasma vs Prolotherapy in the Management Of Knee Osteoarthritis: Randomized Placebo-Controlled Trial

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ABSTRACT

Objective: Osteoarthritis (OA) is an age-dependent disease caused by degenerative and healing processes in subchondral tissue of articular and bone cartilage, resulting in an alteration of its biomechanical properties that eventually causes pain, stiffness, and decreased articular function. The aim of this study is to compare the in vivo the efficacy of platelet-rich plasma (PRP) and prolotherapy with that of placebo in the treatment of knee osteoarthritis(OA).

Materials and Methods: From January 2015 to September 2015, 100 consecutive patients who had a history of chronic (>3 months) pain or swelling radiographically documented grades I to III gonarthrosis (graded according to the Kellgren–Lawrence classification scale for tibiofemoral joint degeneration) were enrolled. The exclusion criteria included severe OA (grade IV according to the Kellgren–Lawrence classification (22)), received an intra-articular injeciton of hyalurinic acid agents within 6 months, previous lower extremity surgery, systemic disorders (diabetes, rheumatic diseases, severe cardiovascular diseases, haematological diseases, infections), presence of any concomitant knee lesion causing pain or swelling. In this randomized placebo-controlled clinical trial patients with knee osteoarthritis were randomly assigned into 3 groups: participants in Group 1 received prolotheraphy, participants in Group 2 received intra-articular injections of PRP and participants in Group 3 received saline injection. Demographic findings and Western Ontario and McMaster Universities arthritis index (WOMAC) were recorded before each injection and 3 and 6 months after the first injection.

Results: Group 1 comprised 20 patients with a mean age 66,00±5,79, Group 2 comprised 18 patients with a mean age 64,16±6,36 and Group 3 comprised 20 patients with a mean age 62,00±6,46. Groups were similar in terms of age, gender and body mass index (p>0,05). Baseline total WOMAC scores and WOMAC subscales of the groups were also similar (p>0,05). Although total WOMAC scores and WOMAC subscales improved in Group 1 and Group 1 after treatment, none of these improvements reached statistical significance

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(p>0,05). Moreover, post-treatment total WOMAC scores and subscales of WOMAC were similar in all groups (p>0,05).

Conclusion: Our findings does not support the use of PRP or prolotherapy as a first- or second-line treatment for knee OA.

Key words: Knee osteoarthritis, platelet-rich plasma, prolotherapy

Diz Osteoartritlerinin Tedavisinde Trombositten Zengin Plazma Ve Proloterapi Uygulamalarının Karşılaştırılması; Randomize Plasebo Kontrollü Çalışma

ÖZ

Amaç: Osteoartrit yaşa bağlı olarak, eklemin subkondral dokusunun ve kemik kartilajın dejenerasyonu ve iyileşmesi süreciyle devam edip eklem biyomekaniğinin bozulmasıyla seyreden, sonuç olarak da eklemde ağrıya, katılığa ve azalmış eklem fonksiyonuna neden olan kronik bir hastalıktır. Bu çalışmanın amacı diz osteoartritinde plateletten zengin plazma ve proloterapi tedavisinin kontrol grubuyla kıyaslanarak etkinliğinin karşılaştırılmasıdır.

Gereç ve Yöntemler: Ocak 2015-Eylül 2015 tarihleri arasında, dizlerinde 3 aydan daha uzun süreli ağrı ve şişlik şikayeri olan,radyolojik olarak (Kelgren-Lawrence tibiofemoral eklem dejenerasyon sınıflaması) evre 1-3 olarak dokümente edilmiş 100 diz osteoartriti tanısı almış hasta grubu çalışmaya dahil edildi.Grade 4 vakalar,son 6 ay içinde eklem içi hyaluronik enjeksiyon almış olanlar,alt ekstremite cerrahisi geçirmiş olanlar, diyabet,romatolojik hastalık,ciddi kardiovasküler hastalığı olanlar çalışma dışında tutuldu. Vakalar 3 gruba ayrıldı. Grup 1; Proloterapi uygulanan, Grup 2; PRP uygulanan, Grup 3; serum fizyolojik uygulanan (plasebo) grubu olarak isimlendirildi. Demographic bulgular ve Western Ontario and McMaster Universities arthritis (WOMAC) skorları, enjeksiyon öncesi, sonrası 3 ve 6. Ay olarak kaydedildi.

Bulgular: Grup1 yaş ortalaması 66,00±5,79 olan 20 hastadan , Group 2 yaş ortalaması 64,16±6,36 olan 18 hastadan ve Group 3 ise yaş ortalaması 62,00±6,46 olan 20 hastadan oluşmaktaydı. Gruplar,yaş cinsiyet ve vücut kitle indeksi olarak benzerdi. (hepsi p>0,05). Bazal toplam WOMAC skorları ve WOMAC altgrup skorları da benzerdi. (p>0,05). Toplam WOMAC ve alt grup skorları Grup 1'de tedavi öncesine göre gelişim göstermesine rağmen hiçbir grupta istatistiksel olarak anlamlı değildi (p>0,05). Bunun yanında tedavi sonrası bütün gruplarda WOMAC toplam ve alt grup toplam skorları bütün gruplarda benzerdi (p>0,05).

Sonuç: Sonuçlarımız, PRP ve Proloterapi uygulamasını diz osteoartriti açısından ilk ve ikinci basamak tedavi seçeneği olarak desteklememektedir.

Anahtar sözcükler: Diz osteoartriti, plateletten zengin plazma, proloterapi

INTRODUCTION

Osteoarthritis (OA) is an age-dependent disease caused by degenerative and healing processes in subchondral tissue of articular bone cartilage, resulting in an alteration of its biomechanical properties that eventually causes pain,

stiffness, and decreased articular function(1,2). It is the most common of all joint diseases and exacts a heavy economic toll due to its high prevalence in the general population and potential for causing progressive disability (2). To date, the pharmacological armamentarium for OA is confined to symptomatic treatments, whose goal is to diminish functional impairments and pain severity(3).

In older patients, who are refractory to conservative management, knee replacement surgery is the primary intended treatment for severe knee OA to relieve pain and improve function (4). Owing to the limited lifespan of joint replacements with implant wear and the associated risk for joint revision, new nonoperative options are being proposed to treat earlier stages of joint degeneration to provide symptomatic relief and delay surgical intervention in the younger and middle-aged population with cartilage damage and OA of the knee.

Among these, a novel biological treatment approach, platelet-rich plasma (PRP), has been introduced into clinical practice as a minimally invasive solution to improve the status of the joint surface and allow a fast return to full activity (5-15). The other one is the prolotherapy, also known as proliferative therapy, or regeneration injection therapy, is a complementary injection treatment for musculoskeletal conditions including knee OA, that has been hypothesized to stimulate healing of chronic soft-tissue injury (16-21).

In the past several years, a growing body of evidence has accumulated examining PRP and prolotherapy as a possible treatment of knee OA (5-21). However, to the best of the authors' knowledge, there are no data comparing the efficacy of PRP and prolotherapy in treatment of knee OA. Accordingly, the aim of this first randomized placebo-controlled trial was to compare the in vivo efficacy of PRP and prolotherapy with that of placebo in the treatment of knee OA.

MATERIAL AND METHODS

The present randomized placebo-controlled trial was approved by the hospital ethics committee and all the participants consented the study.

Patients

Between January 2015 and September 2015, 100 patients who had a history of chronic (>3 months) pain or swelling, radiographically documented grades I to III gonarthrosis (graded according to the Kellgren–Lawrence classification scale for tibiofemoral joint degeneration) were enrolled. The exclusion criteria included severe OA (grade IV according to the Kellgren–Lawrence classification (22)), received an intra-articular injeciton of hyalurinic acid agents within 6 months, previous lower extremity surgery, systemic disorders (diabetes, rheumatic diseases, severe cardiovascular diseases, haematological diseases, infections), presence of any concomitant knee lesion causing pain or swelling (i.e. ligamentous or meniscal injury), inflammatory arthropathy, immunodepression, therapy with anticoagulants or antiaggregants, use of nonsteroidal anti-inflammatory drugs in the 5 days before blood donation, and hemoglobin count lower than 11 g/dL and platelet count lower than 150,000/mm3.
The patients were randomly assigned into 3 groups: participants in Group 1 received prolotheraphy, participants in Group 2 received intra-articular injections of PRP and parcticipants in Group 3 received saline injection (Fig. 1 – Flow diagram).
The participants were recommended to take acetaminophen 500 mg if needed and were advised on relative rest for 2–3 days.

Table 1: Demographic data of the patients.

	Group 1 (Prolotherapy group, n:20)	Group 2 (PRP group, n:18)	Group 3 (Placebo group, n:20)	p
Age (years)	66,00±5,79	64,16±6,36	62,00±6,46	0,147
Gender				0,055
Male (n)	1	3	1	
Female (n)	19	15	19	
BMI (kg/m^2)	28,7	29,2	29,5	0,133

PRP, platelet-rich plasma; BMI, body mass index.

They were also advised not to use nonsteroidal anti-inflammatory drugs during the following 2 weeks because of their inhibitory effects on the recovery process. They were also discouraged from taking physical therapy during the 6-month follow-up period because of its confounding effect on evaluating research in our essential treatment.

Prolotherapy Preparation and Injection

All participants in Group 1 received dextrose prolotherapy 3 times with 3 weeks interval. The injector examined the knee, marked tender anterior points, injected intradermal skin wheals of 1% lidocaine, and performed prolotherapy injections. Extra-articular injections were done on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 22.5 mL of solution. The 6-mL intra-articular injection was then delivered using an inferomedial approach.

PRP Preparation and Injection

The PRP specimens were collected as described by Filardo et al.(23) from all the participants in Group 2. A total of 100 mL of venous blood (collected in a bag containing 15 mL of sodium citrate) was collected under aseptic conditions from the antecubital vein. Additionally, a peripheral blood count was obtained. To collect 12 mL of PRP, two centrifugations (the first at 1500 rpm for 6 min and the second at 3500 rpm for 12 min) were performed. The PRP unit was divided into 2 small units of 6 mL each: 1 unit was sent to the laboratory for a platelet count as well as concentration and bacteriological tests, 1 unit was used for injection within 2 hours.

The injections were administered 3 times with 3 weeks interval. The same method was used for second injection. Before the injection, the PRP was activated by adding 10% calcium chloride. The preparation method used allowed the number of platelets per milliliter to increase by means of 4,5 ± 1,3 times with respect to baseline blood values. Leukocytes were also present, with a mean concentration of 1,2 ± 0,6 times with respect to the normal blood value.

Placebo Injection

All the participants in Group 3 received 0,09% NaCl 3 times with 3 weeks interval with the same injection amounts and method as in prolotherapy group.

Outcome Measures

Baseline demographic findings and Western Ontario and McMaster

Universities arthritis index (WOMAC) were recorded(24). The patients were evaluated for these parameters 1 hour before each injection and 3 and 6 months after the first injection.

The WOMAC questionnaire is used to evaluate a patient's functions when diagnosed with rheumatic diseases, especially knee OA. The WOMAC is a 24-item questionnaire with three subscales measuring pain (five items), stiffness (two items), and physical function (17 items). Answers to each of the 24 questions are scored on five-point Likert scales (none = 0, slight = 1, moderate = 2, severe = 3, extreme = 4), with total scores ranging from 0 to 96. So, the maximum possible scores for WOMAC, pain, stiffness, and function are 96 (most severe), 20, 8, and 68, respectively(24). Higher scores indicate greater disease severity. WOMAC questionnaire is performed by an independent physician who is blind to the injection groups.

Statistical Analysis

Data were analysed using SPSS v.15.0 for Windows. Descriptive statistics are given as mean standard deviation (SD) and quantities. Kolmogorov-Smirnov Test was used to determine whether data followed a normal distribution. Statistical comparisons were carried out with chi-square ($\chi 2$), Wilcoxon signed rank test and Mann Whitney-U tests. The study has a power of 80%. The level of significance was set at $p<0,05$.

RESULTS

Of the 100 persons evaluated 60 met eligability ciriteria and were enrolled and randomized(Figure 1). 2 patients from Group 2 discontinued the study due to changing accommodation. Group 1 comprised 20 patients (1 male and 19 females) with a mean age 66,00±5,79 years, Group 2 comprised 18 patients (3 males and 15 females) with a mean age 64,16±6,36 years, and Group 3 comprised 20 patients (1 male and 19 females) with a mean age 62,00±6,46 years. No severe adverse events were reported in any participants.

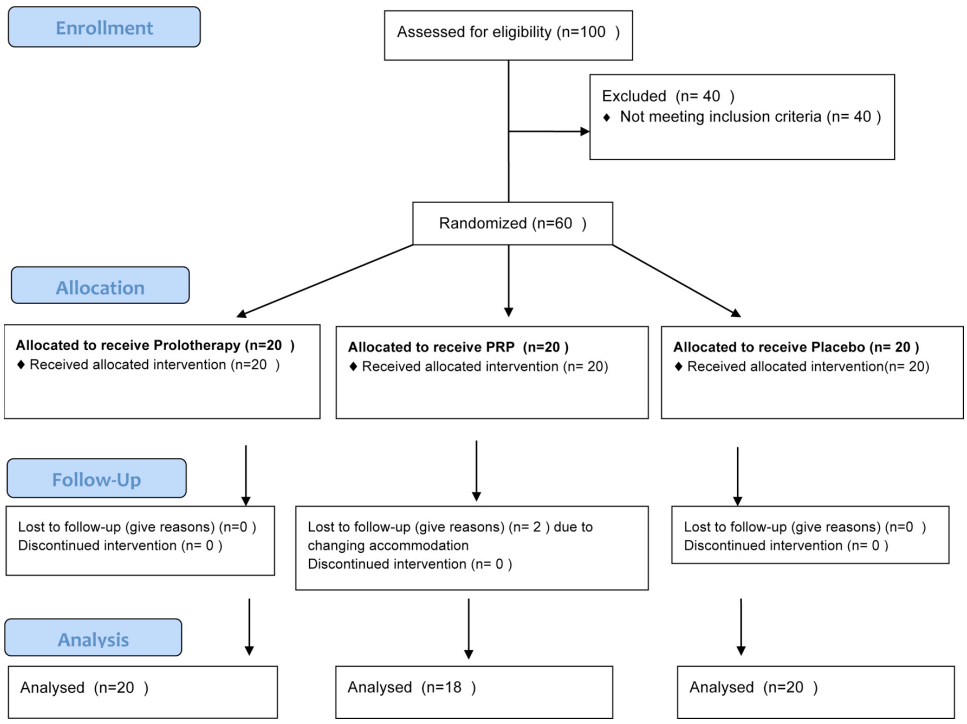

Figure-1. Flow Diagram of the study. PRP, Platelet-Rich Plasma

Table 2: Western Ontario and McMaster Universities arthritis index scores of the patients.

	Group 1		Group 2		Group 3		G 1 vs G2	G 1 vs G2	G 1 vs G2
	Mean (SD)	***P*[a]**	**Mean (SD)**	***P*[a]**	**Mean (SD)**	***P*[a]**	***P***	***P***	***P***
Pain									
Baseline	7,00 (4,20)		6,88 (4,22)		7,10 (4,20)		0,874	0,965	0,874
Before 2nd injection	6,15 (3,63)	0,101	6,33 (3,54)	0,128	6,70 (3,74)	0,059	0,897	0,602	0,718
Before 3rd injection	5,75 (3,28)	0,054			6,85 (3,99)	0,180		0,445	
At 3 months	5,80 (3,38)	0,057	6,11 (3,14)	0,097	6,80 (3,89)	0,170	0,880	0,478	0,675
At 6 months	5,35 (3,39)	0,079	6,38 (2,25)	0,965	6,90 (4,06)	0,157	0,239	0,314	0,942
Stiffness									
Baseline	2,40 (2,11)		2,22 (2,04)		2,50 (2,21)		0,828	0,887	0,828
Before 2nd injection	2,20 (1,64)	0,221	2,16 (1,72)	0,341	2,35 (2,03)	0,317	0,965	0,841	0,806
Before 3rd injection	2,20 (1,43)	0,408			2,25 (1,88)	0,181		0,883	
At 3 months	2,10 (1,51)	0,205	2,30 (1,78)	0,350	2,30 (1,98)	0,280	0,942	0,758	0,874
At 6 months	2,85 (1,49)	0,325	2,55 (1,04)	0,325	2,40 (2,18)	0,305	0,331	0,369	0,593
Function									
Baseline	24,10 (9,58)		24,22 (9,64)		23,10 (9,83)		0,938	0,602	0,613
Before 2nd injection	22,75(10,2)	0,106	23,05 (10,44)	0,187	22,35 (9,37)	0,177	0,919	0,904	0,828
Before 3rd injection	21,70 (9,47)	0,053			22,65 (9,74)	0,166		0,678	
At 3 months	22,45 (8,88)	0,058	22,55 (9,69)	0,147	23,25 (9,34)	0,406	0,830	0,738	0,874
At 6 months	22,50 (8,85)	0,092	22,22 (9,77)	0,492	22,85 (9,68)	0,102	0,828	0,968	0,965
WOMAC total									
Baseline	33,50 (13,72)		33,33 (13,65)		32,70 (13,99)		0,806	0,678	0,897
Before 2nd injection	31,10 (13,90)	0,056	31,55 (14,22)	0,107	31,40 (13,12)	0,103	0,897	0,841	0,919
Before 3rd injection	29,65 (12,75)	0,076			31,75 (13,73)	0,116		0,547	
At 3 months	30,35 (12,08)	0,098	30,96 (13,13)	0,097	32,35 (13,33)	0,968	0,965	0,640	0,675
At 6 months	30,70 (12,53)	0,089	31,16 (12,05)	0,513	32,15 (13,67)	0,084	0,815	0,841	0,888

Womac, Western Ontario and McMaster Universities arthritis index. [a]Compared with baseline.
G1: Group 1 **G2:** Group2

Groups were similar in terms of age, gender and body mass index (p>0,05). Patient demographics are shown in Table I. Baseline total WOMAC scores and WOMAC subscales of the groups were also similar (p>0,05) (Table 2). Although total WOMAC scores and WOMAC subscales improved in Group 1 and Group 2, none of these improvements reached statistically significance (p>0,05) (Table 2). Moreover, post-treatment total WOMAC scores and subscales of WOMAC were similar in all groups (p>0,05) (Table 2).

DISCUSSION

This first randomized placebo-controlled trial comparing the *in vivo* efficacy of PRP and prolotherapy with that of placebo in the treatment of knee OA shows that improvements in PRP, prolotherapy did not reach statistical significance. Moreover, PRP and prolotherapy showed no superiority either to each other or placebo.

The weak potential of joint cartilage repair which is related to its avascular nature has resulted in numerous researches focusing on cartilage repair processes during the last two decades. Common treatments for cartilage tissue repair procure relative satisfaction, but rarely achieve an ideal level of functional capacity for the patients (14). Recently, innovative treatments for cartilage tissue repair have been introduced, including mesenchymal stem cell therapy, autologous chondrocyte implantation, use of matrix metalloproteinase inhibitors, gene therapy and growth factors. PRP and prolotherapy are two innovative treatment methods which have been promised to improve cartilage repair and soft-tissue healing via different ways (25).

PRP is the volume of plasma with a high platelet concentration above normal baseline values. Platelets are sources of high concentrations of cytokines and a group of growth factors which regulate healing processes as well as tissue regeneration. Because platelets have a high concentration of growth factors and cytokines within their alpha granules and dense granules, this makes PRP an appealing therapeutic alternative. Several vital factors found inside the alpha granules of the platelet are platelet-derived growth factor, transforming growth factor-beta, insulin-like growth factor-1, vascular endothelial growth factor, and epidermal growth factor among others(12,26). The dense granules of the platelets also contain neuromodulators and inflammatory mediators such as histamine and serotonin. Platelets are stimulated to release these growth factors and cytokines by exposure either to collagen or to thrombin and calcium. All the aforementioned growth factors and cytokines may have an impact on soft tissue healing and cartilage regeneration. Some prospective studies have been designed to evaluate the effectiveness of PRP on knee OA and have obtained statistically significant improvements in all the clinical scores at the end of therapy (4-15). However, an important limitation of these studies was the lacking of a control group. In contrast to improved results, some prospective studies have concluded that PRP did not affect outcomes (27). According to our results, PRP treatment did not improve clinical parameters. Moreover, PRP treatment showed no superiority to prolotherapy and placebo. The contradictions in PRP studies arise

from various variables; including preparation method, needle gauge for blood harvest and injection, platelet concentration and cellularity, platelet granule secretion variability, leukocyte (and subtype) concentration, platelet storage, anticoagulant use, platelet preactivation, local anesthesia use, image guidance use, injection volume, injection frequency, preinjection and postinjection protocol, severity of OA being treated, and other patient factors and follow-up duration.

Prolotherapy has been reported as a useful method in the treatment of chronic musculoskeletal and joint diseases (16-21). Although, prolotherapy is being inceasingly used worldwide, its mechanism of action is not yet clearly understood. Several mechanisms have been proposed, such as causing mild inflammation and cell stressing in the weakened ligament or tendon area, releasing cytokines and growth factors, and inducing a new healing cascade in that area, which leads to activation of fibroblasts, generation of collagen precursors, and strengthening of the connective tissue. It is also hypothesized that the increased extracellular glucose level and the contact of human cells with the hypertonic environment causes an increase in multiple growth factors in different cells. By these presumed mechanisms, the hypertonic dextrose solution stimulates the proliferation of chondrocytes, osteocytes, and fibroblasts. These cells then excrete extracellular matrix, which enhances the stability of the joints by tightening and strengthening the ligaments, tendons, and joint stabilizing structures (16-21). There are some reports regarding the effects of prolotherapy on OA. These studies have shown an improvement in different pain scales between 36% and 55%, as well as improved WOMAC scores following prolotherapy (17-21). Moreover, one study reports meaningful clinical imrovement with prolotherapy treatment when compared with placebo (19). However, we did not find significant improvement in WOMAC scores of patients who received prolotheraphy. In addition, post-treament clinical scores of the patients who received prolotherapy and placebo were similar. This may result from the limited number of patients in our study as well as preferred guidance (palpation versus image), local anesthetic use, injection volume, injection frequency, preinjection and postinjection protocol (e.g., nonsteroidal anti-inflammatory drugs/activity restriction), type and severity of disease being treated, patient-specific factors (age, sex, platelet disorders), selected method and areas for injection or the different amounts of dilutions of dextrose and follow-up duration.

The present study does have some limitations; primarily the small patient groups with female predominance, and the lack of 12 months' follow-up, as well as the lack of double-blind design. Although questionnaire is performed by an independent physician who is blind to the injection groups, a potential bias would have ensued due to the fact that the physician who performed the injections was not blinded. Besides, lack of femoral cartilage thickness evaluation with ultrasound is an another limitation. Nevertheless, the results appear to be significant.

CONCLUSION

In conclusion, our findings do not support the use of PRP or prolotherapy as a first- or second-line treatment for knee OA. Large multicenter placebo-

controlled randomized clinical trials using a uniform method of administration schedule with long-term follow-up is needed to further assess the efficacy of PRP and prolotherapy treatment for patients with knee OA. Last but not least, changes in femoral cartilage thickness should be screened with ultrasound in further studies.

KAYNAKLAR

1. *Tok F, Aydemir K, Peker F, Safaz I, Taşkaynatan MA, Ozgül A. The effects of electrical stimulation combined with continuous passive motion versus isometric exercise on symptoms, functional capacity, quality of life and balance in knee osteoarthritis: randomized clinical trial. Rheumatol Int. 2011;31:177-81.*
2. *Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465-74.*
3. *Ornetti P, Nourissat G, Berenbaum F, Sellam J, Richette P, Chevalier X, et al. Does platelet-rich plasma have a role in the treatment of osteoarthritis? Joint Bone Spine. 2015. pii:S1297-319X(15)00104-9.*
4. *Hashemi M, Jalili P, Mennati S, Koosha A, Rohanifar R, Madadi F, et al. The Effects of Prolotherapy With Hypertonic Dextrose Versus Prolozone (Intraarticular Ozone) in Patients With Knee Osteoarthritis. Anesth Pain Med. 2015;5:e27585.*
5. *Angoorani H, Mazaherinezhad A, Marjomaki O, Younespour S. Treatment of knee osteoarthritis with platelet-rich plasma in comparison with transcutaneous electrical nerve stimulation plus exercise: a randomized clinical trial. Med J Islam Repub Iran. 2015;29:223.*
6. *Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy. 2015. pii: S0749-8063(15)00659-3.*
7. *Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk 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].*
8. *Kanchanatawan W, Arirachakaran A, Chaijenkij K, Prasathaporn N, Boonard M, Piyapittayanun P, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2015. [Epub ahead of print] .*
9. *Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015;43:1575-82.*
10. *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;7:637-48.*
11. *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;49:657-72.*
12. *Rodriguez-Merchan EC. Intraarticular Injections of Platelet-rich Plasma (PRP) in the Management of Knee Osteoarthritis. Arch Bone Jt Surg. 2013;1:5-8.*
13. *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:S108-21.*
14. *Rayegani SM, Raeissadat SA, Taheri MS, Babaee M, Bahrami MH, Eliaspour D, Ghorbani E. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev (Pavia). 2014;6:5405.*
15. *Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, Azma K. Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord. 20157;8:1-8.*
16. *Slattengren AH, Christensen T, Prasad S, Jones K. PURLs: Prolotherapy: a nontraditional approach to knee osteoarthritis. J Fam Pract. 2014;63:206-8.*
17. *Eslamian F, Amouzandeh B. Therapeutic effects of prolotherapy with intra-articular dextrose injection in patients with moderate knee osteoarthritis: a single-arm study with 6 months follow up. Ther Adv Musculoskelet Dis. 2015;7:35-44.*
18. *Rabago D, Patterson JJ, Mundt M, Zgierska A, Fortney L, Grettie J, et al.Dextrose and morrhuate sodium injections (prolotherapy) for knee osteoarthritis: a prospective open-label trial. J Altern Complement Med. 2014;20:383-91.*
19. *Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. AnnFam Med. 2013;11:229-37.*
20. *Rabago D, Mundt M, Zgierska A, Grettie J. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. Complement Ther Med. 2015;23:388-95.*
21. *Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up.J Altern Complement Med. 2012;18:408-14.*

22. *Kellgren J, Lawrence J. Radiological assessment of osteo-arthrosis. Ann Rheum Dis, 1957;16: 494-502.*
23. *Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi 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.*
24. *Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833-40.*
25. *Napolitano M, Matera S, Bossio M, Crescibene A, Costabile E, Almolla J, et al. Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. Blood Transfus. 2012;10:72-7.*
26. *Rodeo SA, Delos D, Weber A, Ju X, Cunningham ME, Fortier L,et al. What's new in orthopaedic research? J Bone Joint Surg Am. 2010; 92:2491-501.*
27. *Morishita M, Ishida K, Matsumoto T, Kuroda R, Kurosaka M, Tsumura N. Intraoperative platelet-rich plasma does not improve outcomes of total knee arthroplasty. J Arthroplasty. 2014;29:2337-41.*