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Comparative study between clinical outcomes of osteoarthritis of knee treated with intra-articular injections of platelet rich plasma and hyaluronic acid

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Abstract

Background: Osteoarthritis (OA) is the most prevalent form of arthritis in the world. With the Progressive ageing of the population, it becomes a major problem of public health. Osteoarthritis is a degenerative affection characterised by many disorders leading to structural and functional defect of one or several joints. OA incidence increases steadily with age, affecting 12.1% of the population from 25 to 74 years old, and it is the leading cause of physical disability in people older than 65 years

Objectives

- To Assess the Clinical Outcomes of Patients with Primary Osteoarthritis of Knee receiving Intra-articular injections of Platelet Rich Plasma and High Molecular Weight Hyaluronic Acid using 'WOMAC' scores, 'IKDC' scores and 'VAS' pain scales
- To compare the Clinical Outcomes between patients receiving Intra-articular PRP and HMW Hyaluronic Acid

Materials and Methods

Methodology: 44 Patients with primary OA of knee, were divided into two groups of 22 each. One group was administered intra-articular injections of PRP and the other group was administered intra-articular injections of Hyaluronic Acid. The functional outcome was assessed before administration of injection and at 6 months follow-up using subjective questionnaire scoring systems i.e. WOMAC, IKDC and VAS indices.

Results: Out of the 44 patients, 33 were females, and 11 males. The average age of patients in Group A was 51.55±6.93 years and 53.27±7.73 years in Group B. 68.2% of patients in the study had bilateral affection. The mean duration of symptoms at time of presentation was 17.27±10.71 months in Group A and 23.64±14.12 months in Group B. The Improvement in functional outcome scores in Group A (WOMAC- 12.980, $P<0.001$; IKDC-11.680, $P<0.001$; VAS- 2.773, $P<0.001$) were significantly better than that of Group B (WOMAC- 6.685, $P<0.001$; IKDC-8.501, $P<0.001$; VAS- 1.773, $P<0.001$)

Conclusion: The results obtained in our study compare well with other studies undertaken in the past. Patients of both groups showed statistically significant improvement in functional outcome at 6months follow-up. The functional outcome of patients receiving Platelet Rich Plasma was significantly better than those receiving Hyaluronic Acid. Therefore PRP is superior to HA in alleviating symptoms and improving short outcome of Kellegren Lawrence Grade 1 and 2 Osteoarthritis Knee. Hence Intra-articular PRP Injections can be considered a safe, simple and efficacious option over that of Hyaluronic Acid in conservative management of Osteoarthritis of Knee.

Keywords: Osteoarthritis, platelet rich plasma, hyaluronic acid, intra-articular injection, WOMAC scale, IKDC scale, VAS scale

Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis in the world. With the progressive ageing of the population, it becomes a major problem of public health. Osteoarthritis is a degenerative affection characterised by many disorders leading to structural and functional defect of one or several joints. OA incidence increases steadily with age, affecting 12.1% of the population from 25 to 74 years old, and it is the leading cause of physical disability in people older than 65 years^[1].

The terms Osteoarthritis and osteoarthrosis (also called Chondromalacic Arthrosis, degenerative arthritis, hypertrophic arthritis, arthritis deformans) are currently used to define

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an idiopathic, slowly progressive disease of diarthrodial (Synovial) joints, occurring late in life and characterized pathologically by focal degeneration of articular cartilage, subchondral bone thickening (Sclerosis), marginal osteochondral outgrowths (Osteophytes) and joint deformity ; Clinically by recurring episodes of pain, synovitis with effusion, stiffness, and progressive limitation of motion; and radiographically by narrowing of joint interval, increased density and thickening of subchondral bone, subchondral cysts, and marginal bony excrescences [2].

PRP can be defined as the volume of the plasma fraction from autologous blood with a platelet concentration above baseline count (200 000 platelets/ μ L) [3]. The platelet concentrate is activated by addition of calcium chloride, and this results in the formation of platelet gel and the release of growth factors and bioactive molecules [4]. Thereby, platelets actively participate in healing processes by delivering a broad spectrum of GFs (insulin-like growth factor, transforming growth factor b-I, platelet derived growth factor, and many others) and other active molecules (e.g. cytokines, chemokines, arachidonic acid metabolites, extracellular matrix proteins, nucleotides, ascorbic acid) to the injured site [5]. These factors altogether contribute to comprehensive roles of PRP, including chondrogenesis, bone remodelling, proliferation, angiogenesis, ant inflammation, coagulation and cell differentiation [6,7].

The rationale for the use of PRP is to stimulate the natural healing cascade and tissue regeneration by a "supraphysiologic" release of platelet-derived factors directly at the site of treatment [1]. However, the clinical efficacy of PRP still remains under debate, and a standardized protocol has not yet been established

Hyaluronic Acid is a naturally occurring glycosaminoglycan and a component of Synovial Fluid and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize Hyaluronic Acid and secrete into the joint. Hyaluronic Acid enhances viscosity and elastic nature of Synovial Fluid [8].

In the recent studies comparing PRP and HA, Kon *et al.* [9]. studied PRP versus HA injections in 150 patients, with PRP treatment giving better results than HA in reducing pain and symptoms and recovering articular function upto 6 months.

Also, Spakova *et al.* [10]. compared 120 patients receiving IA injection of either HA or PRP. The authors reported that statistically and significantly better scores were recorded in the group of patients who received PRP injections after a 3- and 6-months of follow-up.

Hence this study is aimed to compare the clinical outcome between intra-articular injections of Platelet Rich Plasma and high molecular weight Hyaluronic Acid in patients with Primary Osteoarthritis of Knee joint and to establish a protocol for PRP administration in OA.

Materials and Methods

Prospective study of 44 patients (aged above 30 years) with clinical and radiological diagnosis of Osteoarthritis of Knee Joint (Unilateral/ Bilateral) was conducted during the period between November 2015 to October 2017 in the department of Orthopaedics, Bangalore Medical College and Research Institute, Bangalore

- After obtaining institutional ethics committee clearance and written informed consent (Annexure-1), patients attending the OPD of Orthopaedics department, satisfying the inclusion/ exclusion criteria, were enrolled in the study.
- Demographic Data, Brief medical history were be taken,

along with Clinical Examination (Annexure-2) and Routine Investigations (i.e. Complete Blood Count, Serology, Bleeding and Clotting Time, RA factor, ASLO, CRP, ESR, Serum Uric Acid Levels) were done for all the patients enrolled in the study.

- Radiological Investigation and OA Staging- Anteroposterior and Lateral Radiographs of Both Knees in standing position (Stress view) was done for all patients. Based on Kellegren-Lawrence system of grading (Annexure-5), the radiological staging of OA was done for each patient. Patients with KL Grades 3 & 4 were excluded from the study
- Documentation of Baseline Functional Outcome of the affected knee/ knees was done using
 - Western Ontario and McMaster Universities(WOMAC)Score- Annexure-3
 - International Knee Documentation Committee (IKDC) score- Annexure-6
 - Visual Analogue Scale. Annexure- 4
- Then the patients were divided into two groups, i.e A & B, based on each patient's preference and financial affordability.

Patients belonging to Group A were be administered a single intra-articular injection of 6ml of Platelet Rich Plasma (PRP). Autologous PRP was prepared using the single-spin technique as described by Anitua *et al.* i.e Blood extraction was performed in the pre-surgical area using a vacuum system. A total of 20 ml of blood (4 samples of 5 ml) per patient was collected in sterile sodium citrate tubes. The tubes with citrated blood were centrifuged at 1,800 rpm for 8 min to obtain a 6ml concentrate of platelets suspended in plasma, which was separated into three fractions.



Fig 1: Phlebotomy of 20ml of Venous Blood done using Scalp Vein Kit under sterile precautions]



Fig 2: Centrifuge used for Study. Centrifugation @1800rpm for 8 mins



Fig 3: Supernatant PRP after centrifugation (Single-spin Technique)

- Pipetting was carried out with extreme care in all steps, particularly in the last fraction where, to avoid inflammation, leukocytes present in the lowermost portion of the centrifuged plasma is not aspirated. All the steps of open transfer of fluids from the sterile citrated sample tubes were carried out carefully in Laminar Flow Chamber, with sterile disposable gloves and mask to ensure the sterility of the PRP Preparation. Once prepared, the PRP was administered within 30mins without any prior activation (using UV rays, etc).
- Patients belonging to Group B were administered a single intra-articular injection of High Molecular weight Hyaluronic Acid. The molecule used in this study was Hylasto (Zydus Synovia). It is commercially available as sterile pre-filled glass syringes containing 6ml of High Molecular Weight Hyaluronic Acid (8mg/ml).
- Patients of both groups were administered the respective Intra-articular Injections (PRP or HA) in Major OT Complex only, after thorough scrubbing, painting with Betadine followed by Surgical Spirit, and Draping of the knee to be injected. These sterile precautions were meticulously followed for all patients to prevent Septic arthritis, one of the most dreaded complications, resulting from Intra-articular Injections.



Fig 4: All intra-articular injections were administered in Major OT Complex to ensure sterility of environment during procedure]



Fig 5: Thorough Scrubbing and Painting of the Knee Prior to Injection

Superolateral Approach- for the Superolateral approach, the patient lies supine with the knee almost fully extended with a thin pad support underneath the knee to facilitate relaxation. The thumb is used to gently rock then stabilize the patella while the needle is inserted underneath the Superolateral surface of the patella, aimed toward the center of the patella, and then directed slightly posteriorly and infer medially into the knee joint.



Fig 6: Hylasto Injection Administered through Superolateral Approach]



Fig 7: Freshly Prepared PRP Injection Administered via Superolateral Approach

Point of Entry- Lockman reported the concept of the triangle with reasonable accuracy, in which one line is drawn from the apex of the patella (the apex of the triangle) to the lateral pole of the patella and another line is drawn from the apex to the medial upper pole of the patella, resulting in an inverted triangle. The base of the triangle forms the upper border of the patella. The lateral line of the triangle is then marked at the midpoint, where the needle can be inserted [63].



Fig 8: Point of Entry for Superolateral Approach as described by Lockman

- **Post procedural Care:** Patient Vitals were monitored for 30mins after infiltration, to observe for any sudden drop in BP, tachycardia, allergic reactions etc. Patients were advised a temporary course of Analgesics and Oral Antibiotics for 1week. Cold pack compresses used to alleviate immediate post-procedural pain. Patients were allowed to go home on the same day with full weight bearing ambulation advice.
- **Follow up:** All patients in the study were followed up only once, at 6 months interval after the Intra-articular injection. At follow-up, a repeat of patient’s Brief Clinical History, Clinical Examination, Radiograph of Both Knees, and Documentation of all three functional outcome indices (i.e WOMAC, IKDC, VAS Scores) were taken.

Statistics

Majority of the patients in both groups of the study belonged to the age group of 40-50yrs & 51-60yrs, with Mean age ± SD being 51.55±6.93 and 53.27±7.73 in Group A & B, respectively.

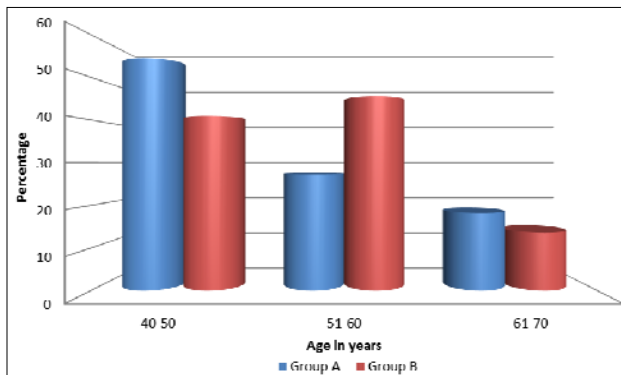


Fig 9: Age distribution of patients studied

Table 1: Duration of Symptoms in months

Duration of Symptoms in months	Group A	Group B	Total
<6	2 (9.1%)	1 (4.5%)	3 (6.8%)
6-12	8 (36.4%)	6 (27.3%)	14 (31.8%)
12-24	8 (36.4%)	8 (36.4%)	16 (36.4%)
>24	4 (18.2%)	7 (31.8%)	11 (25%)
Total	22 (100%)	22 (100%)	44 (100%)
Mean ± SD	17.27±10.71	23.64±14.12	20.45±12.80

P=0.100, not significant, student t test

Results

The primary parameters used for the evaluation of outcome in this study are the WOMAC, IKDC and VAS scores. Evaluation of all the patients included in the study with respect to history, physical findings and post-injection complications in line with the predetermined objectives was done. All the cases in both the groups were followed for a period of 6 months. The patients were followed up at, three monthly, six monthly intervals for any complication or recurrence.

The IKDC scores in patients of both groups of our study showed a statistically significant improvement ($P > 0.001$), during the 6th month follow-up. However the amount of improvement shown by patients in Group A (11.680) was more than that of Group- B. (8.501)

Table 2: IKDC Score distribution in two groups of patients studied

IKDC Score	1 st visit	2 nd visit	% difference
Group I (n=22)			
• <30	0 (0%)	0 (0%)	0.0%
• 30-60	20 (90.9%)	8 (36.4%)	-54.5%
• >60	2 (9.1%)	14 (63.6%)	54.5%
Group II (n=22)			
• <30	1 (4.5%)	1 (4.5%)	0.0%
• 30-60	14 (63.6%)	11 (50%)	-13.6%
• >60	7 (31.8%)	10 (45.5%)	13.7%
P value	0.069*	0.364	-

Chi-Square/Fisher Exact Test

The WOMAC scores in patients of both groups of our study showed a statistically significant improvement ($P > 0.001$), during the 6th month follow-up. However the amount of improvement shown by patients in Group A (12.980) was more than that of Group- B. (6.685). The Difference in the Improvement (6.295) between the 2 groups was statistically significant ($p < 0.001$)

Table 3: WOMAC Score Mean ± SD and P value in two groups of patients studied

WOMAC Score	Group A	Group B	Total	P value
1 st visit	52.65±7.33	50.01±6.54	51.33±7.00	0.213
2 nd visit	39.67±6.55	43.32±6.49	41.50±6.71	0.071+
Difference	12.980	6.685	9.833	0.001**
P value	<0.001**	<0.001**	<0.001**	-

Between group: Student t test (Unpaired); With In group: Student t test (paired)

The VAS scores in patients of both groups of our study showed a statistically significant improvement ($P > 0.001$), during the 6th month follow-up. However the amount of improvement shown by patients in Group A (2.773) was more than that of Group- B. (1.773). The Difference in the Improvement (1.0) between the 2 groups were statistically significant ($p < 0.001$)

Table 4: VAS Scale distribution in two groups of patients studied

VAS Scale	Group A	Group B	Total	P value
1 st visit	7.18±0.80	7.32±0.78	7.25±0.78	0.569
2 nd visit	4.41±0.91	5.55±0.96	4.98±1.09	<0.001**
difference	2.773	1.773	2.273	<0.001**
P value	<0.001**	<0.001**	<0.001**	-

Between group: Student t test (Unpaired); With In group: Student t test (paired)

Discussion

Osteoarthritis (OA), the most common form of arthritis, is a chronic disease characterized by the slow degradation of cartilage, pain, and increasing disability. The disease can have an impact on several aspects of a patient’s life, including functional and social activities, relationships, socioeconomic status, body image, and emotional well-being [11]. It is one of the crucial musculoskeletal disorders characterised by the imbalanced homeostasis and destruction of the articular cartilage, in which pro-inflammatory cytokines are important catabolic regulators during OA cascade [12]. Currently available pharmacological therapies target palliation of pain and include analgesics (i.e. acetaminophen, cyclooxygenase-2-specific inhibitors, nonselective non-steroidal anti-inflammatory drugs, tramadol, opioids), intra-articular therapies (glucocorticoids, hyaluronic acid, PRP), and topical treatments (i.e. capsaicin, methyl salicylate) [13].

Platelet rich plasma (PRP) is a natural concentrate of autologous growth factors from the blood. Platelets actively participate in healing processes by delivering a broad spectrum of GFs (insulin-like growth factor, transforming growth factor b-I, platelet derived growth factor, and many others) and other active molecules (e.g. cytokines, chemokines, arachidonic acid metabolites, extracellular matrix proteins, nucleotides, ascorbic acid) to the injured site. There is experimental evidence for positive effects of PRP in the context of soft tissue healing, ligament and bone regeneration, and inflammation reduction. The application of PRP to treat OA of the knee can be considered a relatively new therapeutic indication [14].

Intra-articular treatment with HA and Hylan has recently become more widely accepted in the armamentarium of therapies for OA pain. HA is responsible for the viscoelastic properties of synovial fluid. The synovial fluid contains a lower concentration and molecular weight (MW) of HA in osteoarthritic joints than in healthy ones. Thus, the goal of intra-articular therapy with HA is to help replace synovial fluid that has lost its viscoelastic properties. The efficacy and tolerability of intra-articular HA for the treatment of pain associated with OA of the knee have been demonstrated in several clinical trials [15].

Table 5: Comparison of WOMAC Scores with other studies

Similar Studies	PRP Group		HA Group	
	Initial	Follow-up	Initial	Follow-up
Present Study	52.65	39.67	50.01	43.32
Raeissadat <i>et al.</i>	39.5	18.44	28.69	27.46
Vaquerizo <i>et al.</i>	45.9	30.8	50.8	54.2
Sánchez <i>et al.</i>	33.9	24.8	29.3	25.9
Spakova <i>et al.</i>	38.76	18.85	43.21	30.90

In the study conducted by Raeissadat *et al.*, the follow up period used was 52 weeks (13 Months). The percentage improvement of WOMAC scores from baseline to follow-up was 52% in PRP group and 4.25% in hyaluronic acid group. The HA molecule used in this study was hyalgan and PRP was prepared by double spin technique [16].

Sánchez *et al.* conducted a multicenter, double-blind clinical trial to evaluate and compare the efficacy and safety of PRGF-Endoret (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain), an autologous biological therapy for regenerative purposes, versus hyaluronic acid (HA) as a short-term treatment for knee pain from osteoarthritis. They randomly assigned 176 patients with symptomatic knee osteoarthritis to receive infiltrations with PRGF-Endoret or with HA (3

injections on a weekly basis). They concluded that Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee [17].

Vaquerizo *et al.* conducted a RCT to compare the efficacy and safety of 3 injections of PRGF-Endoret (BTI Biotechnology Institute, Vitoria, Spain) versus one single intra-articular injection of Durolane hyaluronic acid (HA) (Q-MED AB, Uppsala, Sweden) as a treatment for reducing symptoms in patients with knee osteoarthritis (OA). 96 patients with symptomatic knee OA were randomly assigned to receive PRGF-Endoret (3 injections on a weekly basis) or one infiltration with Durolane HA. The rate of response to PRGF-Endoret was significantly higher than the rate of response to HA for all the scores including pain, stiffness, and physical function on the WOMAC, Lequesne index, and OMERACT-OARSI responders at 24 and 48 weeks [18].

In the study conducted by Spakova *et al.*, the follow up period used were 3 months and 6 months. The percentage improvement of WOMAC scores from baseline to follow-up at 6 months follow-up was 51.4% in PRP group and 28.5% in Hyaluronic acid group. The HA molecule used in this study was Erectus and PRP was prepared by single spin technique [10].

Table 6: Comparison of IKDC Scores with other studies

Similar Studies	PRP Group		HA Group	
	Baseline	Follow-up	Baseline	Follow-up
Present Study	51.28±9.75	62.96±8.37	50.21±14.00	58.71±14.01
Filardo <i>et al.</i>	50.2 ±15.7	64.3 ±16.4	47.4 ±14.0	61.0 ±18.2
Hassan <i>et al.</i>	40.9±10.4	74.3±10.2	-	-

In the comparative study by Filardo *et al.*, the follow-up period used was 12 months and the PRP was prepared using double spin technique. The percentage improvement of IKDC scores recorded from baseline to follow-up was 28.1% with PRP and 28.7% with HA. As the values in both groups were similar, a statistically significant superiority of PRP over HA or vice versa in terms of functional outcome, could not be established in this study [19].

Table 7: Comparison of VAS Scores with other studies

Similar Studies	PRP Group		HA Group	
	Baseline	Follow-up	Baseline	Follow-up
Present Study	7.18±0.80	4.41±0.91	7.32±0.78	5.55±0.96
Lana JFSD <i>et al.</i>	7.5	5.0	7.0	3.0
Hassan <i>et al.</i>	5.9±1.3	3.9±1.1	-	-

The study conducted by Hassan *et al.* was to evaluate the clinical outcome of osteoarthritis knee treated with PRP only. Hence the study consisted of only one group and was not comparative study. VAS and IKDC scales were used as functional outcome indices. PRP was prepared by double spin technique. The follow up period of this study was 6 months. The percentage improvement of IKDC scores from baseline to follow-up at 6 months follow-up was 81.67% and that of VAS was 33.9% with PRP injection [20].

Lana JFSD *et al.* conducted a comparative study using PRP prepared by double spin technique and hyaluronic Acid. The follow up intervals used were 1, 3, 6 and 12 months with VAS and WOMAC questionnaires as functional outcome indices. The improvement of indices noted were 33.3% for PRP and 57.14% for HA with respective to VAS scoring [21].

Conclusion

The present study conducted was to evaluate and compare the functional outcome of patients with Kellegren Lawrence grade I and II osteoarthritis knee treated with a single intra-articular injection of platelet rich plasma and high molecular weight hyaluronic acid. The conclusions drawn from this study are enumerated below.

In this study, majority of patients have bilateral affection of knees, with one knee being more symptomatic than the other. Platelet rich plasma and hyaluronic acid both are effective agents for the alleviation of pain and improving functional outcome of osteoarthritis knee. Autologous PRP was prepared using the single-spin technique described by Anitua *et al.*, owing to its advantage over the double spin technique.

In this study, patients of both groups showed an appreciable and statistically significant improvement in functional outcome at 6 months follow-up period as evidenced by the baseline and follow-up values of all three functional indices i.e. WOMAC, VAS and IKDC scales. However the improvement in functional outcome was more with PRP than with that of HA. Furthermore, the difference in improvement between the two group was also statistically significant ($P < 0.001$).

Therefore single dose, intra-articular PRP injection is superior to that of hyaluronic acid in terms of efficacy and improvement in functional outcome of OA knee, though its preparation is technically more demanding. Strict aseptic precautions are to be followed, from phlebotomy till administration of injection, in order to maintain sterility of preparation and prevent complications. The most dreaded complication of intra-articular injections is septic arthritis, which was not reported in patients of either groups of this study.

More number of randomized control trails and multicenter trails need to be undertaken with larger sample sizes to further confirm and veritably establish the clinical protocols, safety, efficacy and regimen for the regular use of PRP in management of grade-I and II osteoarthritis of knee.

Conflict of interest statement-

The authors of this research article i.e Primary Author – Dr. Purushotham. V. Jawaraya and Co-author- Dr. Navneeth Kumar. G.K have no conflict of interest with respect to the work under consideration for publication, or relevant financial activities outside the submitted work.

There is nothing to disclose by both the concerned authors.

References

1. Alberto Gobbi, Georgios Karnatzikos, *et al.* Platelet-Rich Plasma Treatment in Symptomatic Patients with Knee Osteoarthritis: Preliminary Results in a Group of Active Patients; OASI Bioresearch Foundation Onlus, Via GA Amadeo 24, 20133 Milan, Italy. DOI: 10.1177/1941738111431801
2. Turek's Orthopaedic Principles and their applications, 7th edition, by Anil. K Jain, Chapter, 13, 422
3. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P. Not every PR Pgel is born equal: evaluation of growth factor availability for tissues through four PRP-gel preparations. Fibrinet R, RegenPRP-KitR, PlateletR and one manual procedure. Vox Sang. 2009; 97(2):110-118.
4. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004; 91:4-15 [PMID:14691563]
5. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. J Craniofac Surg 2005; 16:1043-1054 [PMID: 16327552]
6. Woodall J, Tucci M, Mishra A, Benghuzzi H. Cellular effects of platelet rich plasma: A study on HL-60 macrophage-like cells. Biomed Sci Instrum. 2007; 43:266-271 [PMID: 17487092]
7. Drengk A, Zapf A, *et al.* Influence of platelet-rich plasma on chondrogenic differentiation and proliferation of chondrocytes and mesenchymal stem cells. Cells Tissues Organs 2009; 189:317-326 [PMID: 18689989 DOI: 10.1159/000151290]
8. Egemen Ayhan, Hayrettin Kesmezacar, Isik Akgun; Intra-articular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop. 2014; 5(3):351-361. doi:10.5312/wjo.v5.i3.351
9. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, *et al.* Platelet- rich plasma intra-articular injection versus hyaluronic acid visco supplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011; 27:1490-1501 [PMID: 21831567 DOI: 10.1016/j.arthro.2011.05.011]
10. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012; 91:411-417 [PMID: 22513879 DOI: 10.1097/PHM.0b013e3182a ab72]
11. Carr AJ. Beyond disability: measuring the social and personal consequences of osteoarthritis. Osteoarthritis Cartilage. 1999; 7:230-238.
12. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther. 2009; 11(3):227
13. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines: Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum. 2000; 43:1905-1915.
14. De La Mata J. Platelet rich plasma a new treatment tool for the rheumatologist? Reumatol Clin. 2013; 9:166-71.
15. Adams ME, Atkinson MH, Lussier AJ, Schulz JI, Siminovitsh KA, Wade JP, *et al.* The role of Visco supplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage. 1995; 3:213-22
16. Seyed Ahmad Raeissadat, Seyed Mansoor Rayegani *et al.* Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders, 2015, 8. doi: 10.4137/CMAMD.S17894
17. Mikel Sánchez, Nicolás Fiz, Juan Azofra, *et al.* A Randomized Clinical Trial Evaluating Plasma Rich in Growth Factors (PRGF-Endoret) Versus Hyaluronic Acid in the Short-Term Treatment of Symptomatic Knee Osteoarthritis. Arthroscopy: The Journal of Arthroscopic and Related Surgery. 2012; 28(8):1070-1078
18. Víctor Vaquerizo, Miguel Ángel Plasencia *et al.* Comparison of Intra-Articular Injections of Plasma Rich in Growth Factors (PRGF-Endoret) Versus Durolane Hyaluronic Acid in the Treatment of Patients with

- Symptomatic Osteoarthritis: A Randomized Controlled Trial. *Arthroscopy: The Journal of Arthroscopic and Related Surgery*. 2013; 29(10):1635-1643
19. Giuseppe Filardo, Elizaveta Kon, *et al.* Platelet-rich plasma vs Hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled Trial. *BMC Musculoskeletal Disorders*. 2012; 13:229. <http://www.biomedcentral.com/1471-2474/13/229>
 20. Ali Soliman Hassan, Abeer Mohamed El-Shafey, *et al.* Effectiveness of the intra-articular injection of platelet rich plasma in the treatment of patients with primary knee osteoarthritis. Elsevier B.V. on behalf of Egyptian Society of Rheumatic Diseases. <http://dx.doi.org/10.1016/j.ejr.2014.11.004>
 21. Lana JFSD, Weglein, Sampson *et al.* Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *Journal of Stem Cells and Regenerative Medicine*. 2016; 12(2):69.