



COMPARISON BETWEEN INTRA-ARTICULAR PLATELET-RICH PLASMA AND CORTICOSTEROID INJECTION UNDER ULTRASOUND GUIDANCE IN THE MANAGEMENT OF PAIN AND IMPROVEMENT OF FUNCTIONAL OUTCOME IN PATIENTS SUFFERING FROM KNEE OSTEOARTHRITIS: A RANDOMIZED CONTROL TRIAL

Orthopedics

Debasish Deb	Post Graduate Trainee, Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences (RIMS), Imphal
Yumnam Nandabir Singh*	Professor and Head, Department of Sports Medicine, RIMS, Imphal *Corresponding Author
Naorem Bimol singh	Assistant professor, Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences (RIMS), Imphal
Rakesh Das	Post Graduate Trainee, Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences (RIMS), Imphal
Shanavas Anoth Meethal	Post Graduate Trainee, Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences (RIMS), Imphal

ABSTRACT

Background: Knee osteoarthritis is one of the most prevalent and disabling diseases worldwide, which decreases patients' quality of life (QoL). However, pharmacological and non-pharmacological treatments, apart from complications, could not desirably control the disease. **Objectives:** The current study aimed at Comparing between Intra-articular Platelet-Rich Plasma and Corticosteroid Injection under Ultrasound Guidance in the management of Pain and improvement of functional outcome in patients suffering from Knee Osteoarthritis. **Methods:** A randomized clinical trial was performed on 67- patients with grades II-III of knee osteoarthritis (OA) coming to RIMS PMR OPD Imphal, from April 2019 to June 2020. Patients were randomly divided into two groups: Triamcinolone (A) (n=34) and PRP (B) (n=33) by quadruple block. In the group A, 40 mg Triamcinolone and in the group B, PRP was injected intra-articularly, under ultrasound- guidance, once a month, for three consecutive months. Patients' pain intensity was evaluated based on the Visual Analog Scale (VAS), and their outcome was determined based on the Knee injury and Osteoarthritis Outcome Score (KOOS) monthly for three consecutive months, as well as six months after the treatment. **Results:** There were no significant differences between the groups regarding demographic characteristics. VAS assessments indicated lower pain scores in the group B than group A; the difference between the groups was statistically significant two, three, and six months after the injections. In the group B, the mean initial VAS was 7.36 ± 0.92 compared with 7.12 ± 1.29 in the group A ($P = 0.385$). After six months, the scores dropped to 3.45 ± 0.86 and 4.81 ± 1.4 , respectively ($P = 0.0001$). Examination of the KOOS parameters showed a significant association between treatment outcomes in the group P than the group T. Therefore, the test showed a significant difference between the groups regarding relief of pain, improvement of symptoms and activities of daily living (ADL) two, three, and six months after treatment. There was also a significant difference between the groups in terms of the quality of life (QoL) and doing sport activities three and six months after the treatment ($P < 0.05$). Based on the repeated measures analysis, a significant inter- and intra-group differences in the mean score of KOOS parameters was observed between the intervals ($P = 0.0001$). **Conclusions:** The current study results showed that three intra-articular injections of Triamcinolone and PRP could reduce pain and improve articular function in patients with grades II-III knee osteoarthritis. However, pain relief and improvement in the outcomes were more effective and more prolonged secondary to PRP injections than corticosteroid

KEYWORDS

INTRODUCTION:

Osteoarthritis (OA) is the joint insufficiency in which all of the joint structures have pathological changes (1). Knee OA is the most common type of OA in the lower extremity and constitutes 23% of all arthritis cases (2). It is probably a polygenic disease that may be affected by environmental factors. Higher age, female gender, overweight and obesity, knee injury, repetitive use of knee, bone density, muscle weakness, and joint laxity are associated with the progression of OA (3, 4). About 13% of females and 10% of males aged above 60 years have symptomatic knee OA (5). In a recent study on rural areas population in Iran, results showed that about 20% of the studied population had OA in at least one of their joints. Also, the prevalence of OA in rural areas population of Iran was higher than those of Asian countries (4). Considering the increase in life expectancy and old population, it is one of the most challenging medical issues, worldwide (1, 6-8). Pain due to the knee or hip OA causes insufficient activity. Since OA is a common disease, inactivity is a public health problem that increases the risk of cardiovascular diseases.

The primary goal of the treatment is to relieve pain and minimize the loss of physical function, and then, inhibit the disease progression in order to maintain the patients' independence and improve their quality of life (QoL). Non-pharmacological (education and diet) and pharmacological (non-opioid oral analgesics) treatments are the initial recommended treatment for OA (9-13). Intra-articular injections can be used as an alternative treatment for oral medications in patients with

poor response to such drugs (14).

Since synovial inflammation is probably one of the major causes of pain in patients with OA, topical anti-inflammatory therapies, administered intra-articularly, are effective to relieve the pain (15). Corticosteroids have anti-inflammatory and immunosuppressive effects, but their mechanism of action is complicated (16). These drugs reduce vascular permeability and inhibit the accumulation of inflammatory cells, phagocytosis, production of superoxide neutrophil, and prevent the synthesis and release of inflammatory mediators such as prostaglandin and leukotrienes (17). The anti-inflammatory effects of these drugs reduce erythema, swelling, warmth, and tenderness of the inflamed joints and increase viscosity by increasing the concentration of hyaluronic acid (18). Despite previous investigations, still, there is no consensus on the type of selected corticosteroid and the optimal dosage (19-21).

It is believed that the progression of OA results from an imbalance between pro-inflammatory cytokines such as interleukin (IL)-1 α , IL-1 β , tumor necrosis factor (TNF)- α , and anti-inflammatory cytokines including IL-4, IL-10, etc. It activates the proteolytic enzymes responsible for joint degeneration. Recently, treatments are used to eliminate this cytokine imbalance. One of these treatments is the use of platelet-rich plasma (PRP) (22). PRP is one of the new therapeutic approaches recently attracted interests and various researches were performed in this field. It is provided from the autologous blood centrifuge and is a volume of plasma containing a high concentration

of platelets and white blood cells (WBCs). WBCs and platelets are the rich sources of cytokines used to regulate a number of healing and tissue regeneration processes. Platelets, in addition to cytokines, contain large amounts of growth factors and also release large amounts of bioactive proteins that increase the removal of necrotic tissues and accelerate the processes of tissue regeneration and healing (23-25). There is strong evidence of the efficacy of PRP in musculoskeletal diseases, wound healing, and OA in previous clinical trials (23, 26-29). However, according to the Filardo et al., there is a need for more organized studies with larger sample sizes to judge the effectiveness of these methods in the management of knee OA (30).

Since knee OA is one of the most prevalent and disabling diseases worldwide, it causes different levels of dysfunction. On the other hand, conventional and non-pharmacological treatments and surgical procedures, apart from complications, cannot optimally control the disease. Therefore, constant efforts to find new therapies with minimal complications and invasiveness and maximum efficacy are in progress (23, 26, 31). Intra-articular injections of PRP and corticosteroids are today popular therapeutic approaches. Although previous studies showed the effectiveness of each method in the treatment of knee OA (23, 26), based on the current review findings, only two studies examined the effectiveness of PRP injection versus intra-articular corticosteroids in the treatment of knee OA (32, 33). These studies administered only single dose of corticosteroid or PRP injection and the results were controversial; no study so far tried to compare the effect of multiple injections of these two compounds on knee OA treatment.

Objectives

The current study aimed at comparing the effect of three intra-articular corticosteroid and PRP injections, as two therapeutic methods, on pain relief and functional improvement of knee OA.

Methods

Setting

The clinical trial was carried out after obtaining approval from the research ethics board RIMS, Imphal. The study was performed on patients with grades II - III of knee OA referring to RIMS PMR OPD from April 2019 to June 2020.

Study Participants

Before the enrollment, the method of the procedures as well as the advantages and disadvantages, the evaluation technique, and the necessary explanations regarding equal chance for attending in each group was given to the participants and informed consents were obtained.

Inclusion Criteria

Inclusion criteria were age 30 - 75 years, diagnosis of grades II - III knee OA according to the criteria of American College of Rheumatology (ACR) (34), or by tibio-femoral radiography based on Kellgren and Lawrence grading scale criteria (35), patients with debilitating knee pain for at least three months not responding to different treatments and causing dysfunction.

Exclusion Criteria

Exclusion criteria were knee joint deformities, cancer, rheumatoid lesions, body mass index (BMI) > 35 kg/m², pregnancy, breastfeeding, acute infection, hemoglobin < 11 g/dL, platelets < 150,000 × 10⁹/L, blood disorders, hemoglobinopathies, uncontrolled diabetes, acute knee pain, history of knee surgery, serious neurologic or psychological disorders, sciatica pain, history of treatment with anticoagulants, treatment of coagulation disorders, and corticosteroid consumption within last three months.

Randomizations

Using quadruple block, patients were assigned to one of the two groups of PRP intra-articular injection (group B) and intra-articular injection of Triamcinolone (group A).

Interventions

In the group B, to prepare PRP under sterile conditions, a 50-mL of blood was taken from an antecubital vein and placed in the centrifuge kit (standard kit) containing citrate phosphate dextrose (CPDA). Blood was centrifuged in standard kit at 1200 rpm for 15 minutes. Then, the sediment (red blood cells) was placed in the first bag and the supernatant (plasma) in the second bag. It was centrifuged again at

2700 rpm for six minutes. After extraction of free platelet plasma, 5 mL of platelet-rich plasma was injected into the knee joint. This procedure was performed once a month for three consecutive months. Before the onset of study, the analysis of platelet counts on complete blood and PRP of five healthy subjects were conducted to confirm the quality of the PRP prepared based on the using method. Using this method, 4- to 6-fold increase in platelet count was obtained. For intra-articular injection of corticosteroids, in group A, 40 mg of Triamcinolone was injected into the patient's knee each month. To perform injections, the patient was placed in the supine position. Under sterile conditions and after putting the linear probe (6 - 12 MHz) at the top of the patella, a sono-visible needle gauge 21 (Sonoace X6) was entered from the superio-lateral quadrant of the patella and directed with in-plane technique under ultrasound - guidance into the knee joint space. Then, the provided solution was injected into the knee. This monthly injection was performed for three times.

In both groups, after injection for through distribution in joint cavities, the anesthesiologist performed 10 passive knee flexion and extension movements. The patients then rested in the supine position for 10 minutes before discharge. In case of any complication, patients were monitored and discharged after full recovery.

Patients were advised to refrain from weight-bearing on the injected knee 24 - 48 hours after injection. To relieve the pain, patients were advised to use cold compresses (three to four times daily each 10 - 15 minutes), and take acetaminophen (500 mg every eight hours). If the pain was not controlled, acetaminophen could be used every six hours. Patients should avoid non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and drugs affecting platelet count and function. Patients were advised to continue activities with mild to moderate intensity and gradually increase their activities based on personal tolerance.

Outcomes Measurement

The intensity of pain and knee function were evaluated based on Visual Analog Scale (VAS), and Knee injury and OA Outcome Score (KOOS) before the onset of treatment, once a month for three consecutive months, and six months after initiation of treatment. In VAS, zero represents pain relief and 10 scores indicate the highest intensity.

The KOOS is a 42-item, self-reporting questionnaire. It has five subscales including symptoms (seven items), pain (nine items), activities of daily living (ADL) (17 items), sport and recreation function (five items), and QoL (four items).

It is scored based on a five-option Likert scale from 0 to 4. Zero indicates the appropriate score and 4 the worst score. Total scores range from 0 to 100 in which 0 shows severe knee impairment and 100 indicates no problem. The higher total score shows lower disability. Reliability and validity of the Persian version of the questionnaire were confirmed by Salavati et al. (36).

The questionnaire was completed for all the patients by a physician who was blind to the type of treatment. Patients were asked to report any complications including pain, swelling, infection, and hematoma during a six-month follow-up.

Statistical Analysis

Normality of quantitative data was assessed by the Shapiro-Wilk test. Data were expressed by descriptive statistics (as the mean ± standard deviation); quantitative data were analyzed by independent test and repeated measures with SPSS software version 21.0 (SPSS Inc., Chicago, IL., USA). The p-value < 0.05 was considered the level of significance and 95% confidence interval (CI) was noted.

Results

The study subjects were selected from 123 patients with knee pain. Of these, 44 patients did not meet the inclusion criteria and seven patients were not interested to participate. The remaining patients were included in the study and allocated to each A and group B. Three patients from the group B and two patients from the group A were excluded from the study. In the group A, two patients were excluded from the study since they did not cooperate for completing the questionnaires at three and six months follow-ups, and finally, 33 and 34 patients were assigned to B and Group A respectively.

In the current study, there was no significant difference between the

groups regarding demographic characteristics including age, gender, body mass index (BMI), and degree of OA

Table 1: Demographic Characteristics of the Patients

Variables	Group A	Group B	P Value
Gender male/female	7/27	5/28	0.56
AGE in year	58.55 ± 8.79	59.09 ± 7.79	0.794
BMI, kg/m ²	27.78 ± 3.29	28.4 ± 2.78	0.414
OA score, Grade II/III	11/23	9/24	0.65

Patients' pain was assessed based on VAS and test results showed a significant difference between the groups, except for baseline measures and one month after the treatment. Pain intensity in the group B was significantly lower than that of the group A. In the group B, the mean of baseline VAS was 7.36 ± 0.92 vs. 7.12 ± 1.29 in the group A. After six months, it was diminished to 3.45 ± 0.86 and 4.81 ± 1.4, respectively (P = 0.0001). Using repeated measures test, a significant difference in the mean intensity of pain was observed between the intervals in each group as well as two groups (P = 0.0001) Table 2

Table 2: Comparison of the groups based on VAS score (Mean ± SD)

Time	Group A	Group B	P Value
T0	7.12 ± 1.29	7.36 ± 0.92	0.385
T1	5.42 ± 1.22	4.9 ± 1.04	0.071
T2	4.72 ± 1.09	4.06 ± 1.04	0.011
T3	4.24 ± 1	3.69 ± 0.88	0.022
T6	4.81 ± 1.4	3.45 ± 0.86	0.0001
P value intergroup	0.0001	0.0001	
P value intragroup	0.0001		

The parameters of KOOS including pain relief, symptoms relief, ADL, QoL, and sport were evaluated in two groups. Assessing the mean of KOOS parameters including pain relief, symptoms relief, and ADL, showed that except for baseline and one month after treatment, there was a significant difference between the groups. Hence, the level of pain reduction and symptoms relief, as well as increased ADL in the Group B was significantly higher than Group A (P < 0.05). Comparison of the mean QoL and sports parameters in KOOS scale showed no significant differences between the groups except for three and six months post-treatment parameters (Table 3). Repeated measurement indicated a significant difference in the mean scores of KOOS parameters between the intervals in each group, as well as the two groups (P = 0.0001)

Table 3: Comparison of the Groups Regarding Changes in KOOS Parameters (Mean ± SD)

Time/Group	Pain Relief		Symptom Relief		ADL		QoL		Sports	
T0										
Group B	35.26 ± 0.17	40.58 ± 0.683	40.5 ± 0.54	18.56 ± 0.43	14.24 ± 0.54					
Group A	8.9	15.17	7.16	15.02	7.71					
T1										
Group B	38.97 ± 12.89	42.12 ± 15.49	41.52 ± 6.3	21.5 ± 15.1	15.44 ± 8.19					
Group A	52.1 ± 0.48	54.43 ± 0.244	52.09 ± 0.32	26.13 ± 0.73	20.6 ± 0.58					
Group B	9.16	12.07	6.22	11.94	6.34					
Group A	50.16 ± 12.95	50.84 ± 12.95	50.56 ± 6.38	25 ± 14.83	19.7 ± 6.95					
T2										
Group B	61.61 ± 7.93	61.58 ± 9.65	59.13 ± 5.26	31.62 ± 0.19	26.51 ± 6.05					
Group A	56.45 ± 10.84	55.56 ± 11.09	53.54 ± 6.93	27.57 ± 13.59	24.11 ± 6.21					
T3										
Group B	67.84 ± 8.7	67.74 ± 7.54	62.47 ± 6.74	34.84 ± 0.02	31.36 ± 5.62					
Group A	60.62 ± 10.01	59.34 ± 10.62	54.45 ± 6.72	28.49 ± 11.93	24.55 ± 5.95					
T6										
Group B	71.63 ± 7.1	70.34 ± 6.71	65.99 ± 6.78	36.36 ± 0.00	33.03 ± 6.48					
Group A	54.65 ± 11.12	55.25 ± 8.58	47.44 ± 6.84	26.1 ± 11.66	19.41 ± 5.87					

Abbreviations: ADL, Activity of Daily Living; QoL, Quality of Life; T, Time after injection (month)

Group A received Triamcinolone and the group B received Platelet-Rich Plasma intra-knee injections. P < 0.05 was considered significant.

No major complications related to the injections were observed during the treatment and follow-up period. The most commonly observed complication was mild to moderate pain in the injection site, not considered as a serious complication.

DISCUSSION

The current study mentioned the effectiveness of both intra-articular injections of PRP and corticosteroid, but patients receiving PRP had a greater and prolonged improvement in pain severity and physical function than those receiving corticosteroids.

The evaluation of patients in the current study was based on VAS and KOOS. VAS only measures the severity of pain, while the KOOS is a simple self-administered instrument that evaluates patient's short- and long-term symptoms and functions.

The current study showed that both an intra-articular corticosteroid and PRP had beneficial effects on reducing the pain based on VAS. In both groups, the pain decreased until the third month. While the reduction of pain in the Group B prolonged for six months; in Group A, the pain increased in the sixth month compared with that of the third month. However, still, the pain level was significantly lower than the baseline, which suggested the effectiveness of both methods to control the symptoms in the patients. Hassan et al., (37) evaluated the efficacy of the PRP method to control symptoms in patients with OA; patients underwent six intra-articular PRP injections at the intervals of one month. Similar to the current study, the improvement of symptoms was observed at the end of the sixth month compared with the baseline values.

In a study by Kilincoglu et al., (38) patients received PRP and hyaluronic acid through injection once a week for three consecutive weeks. Patients' pain was assessed three and six months after injections. In their study, similar to the current study, patients' pain in both groups decreased up to six months. However, in their PRP group, the pain, based on VAS, at the end of the sixth month was lower than that of the current study. The difference could be attributed to the difference in injection intervals (monthly versus weekly), the centrifugation method, and more importantly, the lower grades of OA in their study participants (grades I - II) compared to those of the patients in the current study (grades II-III).

In a study on the effect of intra-articular corticosteroid and hyaluronic acid on the treatment of knee OA, the effect of corticosteroid on pain reduction in a short period was greater than that of the hyaluronic acid, while the long-term effects of hyaluronic acid were greater than that of the corticosteroids (19). Forough et al., (32) compared intra-articular corticosteroid and PRP, similar to the current study, and observed a significant difference regarding the six-month reduction of pain between the two groups; therefore, pain reduction in the PR group B was significantly higher than that of the corticosteroid group. In the current study, the degree of pain reduction was significantly greater in the PRP than the corticosteroid group in the study by Forough et al. This difference might be attributed to the more frequent corticosteroid injections in the current study (three times with one-month intervals) (in contrast to one time in their study). Joshi Jubert et al., (33) compared corticosteroid and PRP; despite the reduction of pain in both groups, there was no significant difference between the groups. This difference might be noted regarding the higher degree of OA in their study (grades III-IV) compared with the current study.

To assess outcomes based on KOOS, the improvement of all parameters of this criterion was observed in the two groups at post-treatment time points, which indicated the effectiveness of both methods to treat knee OA. Although there was no significant difference between the groups in the first and second months regarding the improvement of parameters, improved parameters were noted more from the second and third months to the sixth month in the group B than the group A and indicated a more effective PRP treatment than corticosteroid.

In a systematic review performed to evaluate the effect of PRP injections on the knee OA, six studies were analyzed, and the results showed that PRP compared with placebo and hyaluronic acid in symptomatic OA patients could better improve symptoms for 12 months. From the six studied investigations, five studies compared PRP with hyaluronic acid, one study compared PRP with saline (placebo), and no study compared PRP with corticosteroids (38). Say et al., (39) compared one PRP injection with three injections of hyaluronic acid, and reported a clinical improvement in both groups, although the PRP Group showed better results. However, in a study by Filardo et al. (30), patients received three injections of PRP and intra-articular hyaluronic acid at three-week intervals. Patients were evaluated by the KOOS criteria at baseline as well as 2-, 6-, and 12-month follow-ups. Based on the results, there was no significant difference in the parameters of KOOS between the groups at all the times. The difference between the results of a study by Filardo and those of previous studies might be attributed to freezing PRP after centrifugation; since freezing the PRP solution causes a change in the morphology of cells, decreases platelets function, and reduces the effectiveness of injected PRP.

In a study by Raynauld et al. (40), patients received intra-articular Triamcinolone or saline every three months for two years. In a two-year follow-up, the symptoms of patients and the parameters of the WOMAC score included pain, stiffness, and physical function improved in the corticosteroid group compared with the placebo group without major complications. The results of their study supported the safety of long-term intra-articular steroids injection in patients with symptomatic knee OA. In a study by Forogh et al., (32), intra-articular injections of PRP resulted in prolonged pain relief, as well as improved LDAs and QoL compared with those of corticosteroids. In their study, there was a significant difference between the groups regarding the KOOS score parameters, except the sports parameter. The results were similar to those of the current study. However in the current study, in terms of sports parameter, at three and six months after treatment, PRP provided better statistical results, which might be attributed to more frequent injections of PRP in the present study.

Joshi Jubert et al., (33) showed that the effect of intra-articular PRP in elderly patients with advanced knee OA was equivalent to those of intra-articular corticosteroid injection. In addition to the number of injections that might cause a difference in the current study, the age, gender, weight, and grade of the disease also might affect the outcome of the study. Female gender, age increase, higher OA grade, and higher BMI score are the risk factors for symptomatic knee OA. According to Kon et al. (27), the highest PRP efficacy was observed in young male patients with lower BMI scores and lower OA grades. In a study by Jubert et al., patients with older ages (mean 67 years), higher BMI value (31 kg/m²), and higher grades of OA (III or IV) were evaluated, which could justify the lower effectiveness of PRP in their study. But in the present study, the age of patients (less than 60 years), BMI < 30 kg/m², and OA grade of KL 2 - 3 could affect the outcome of the study and justify the better treatment outcomes for PRP

Study Limitation

One of the limitations of the study was the inability to perform a double-blind study since, in order to blind patients in the group A, researchers had to take blood, which was not ethical. Although patients were aware of their own therapeutic approach, the physician that evaluated the patients was not.

CONCLUSION

Results of the current study showed that three intra-articular injections of corticosteroids and PRP reduced joint pain and improved joint function. However, PRP injections were more effective and prolonged than corticosteroid therapy in terms of reducing pain and improving the outcomes. Up to three months, both treatments reduced pain and improved physical function. From the third month, the effects of PRP on pain relief and outcomes persisted, but in the corticosteroid group, these effects diminished. However, patients had better conditions in both groups at the end of the sixth month compared with the baseline status.

REFERENCES

- Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):355-69. doi: 10.1016/j.cger.2010.03.001. [PubMed: 20699159]. [PubMed Central: PMC2920533].
- Moretti M. Effectiveness of treatment with Oxygen-Ozone and hyaluronic acid in osteoarthritis of the knee. *Int J Ozone Ther*. 2010;9(1):25-9.
- Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):371-86. doi: 10.1016/j.cger.2010.03.002. [PubMed: 20699160]. [PubMed Central: PMC2920876].
- Tehrani-Banihashemi A, Davatchi F, Jamshidi AR, Faezi T, Paragomi P, Barghamdi M. Prevalence of osteoarthritis in rural areas of Iran: a WHO-ILAR COPCORD study. *Int J Rheum Dis*. 2014;17(4):384-8. doi: 10.1111/1756-185X.12312. [PubMed: 24618176].
- Welling P, Evans C, Welling J, Maixner W. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. *Ther Adv Musculoskelet Dis*. 2017;9(8):183-96. doi: 10.1177/1759720X17712695. [PubMed: 28835778]. [PubMed Central: PMC5557186].
- Reid CR, Bush PM, Cummings NH, McMullin DL, Durrani SK. A review of occupational knee disorders. *J Occup Rehabil*. 2010;20(4):489-501. doi: 10.1007/s10926-010-9242-8. [PubMed: 20490901].
- Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15. doi: 10.1016/j.berh.2014.01.004. [PubMed: 24792942].
- Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am*. 2013;39(1):1-19. doi: 10.1016/j.rdc.2012.10.004. [PubMed: 23312408]. [PubMed Central: PMC3545412].
- Brown GA. AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):577-9. doi: 10.5435/JAAOS-21-09-577. [PubMed: 23996989].
- Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. 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(4):465-74. doi: 10.1002/acr.21596. [PubMed: 22563589].
- Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARS recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;18(4):476-99. doi: 10.1016/j.joca.2010.01.013. [PubMed: 20170770].
- Brüery O, Cooper C, Pelletier JP, Branco J, Luisa Brandi M, Guillemin F, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum*. 2014;44(3):253-63. doi: 10.1016/j.semarth.2014.05.014.
- Jevevar DS, Brown GA, Jones DL, Matzkin EG, Manner PA, Moor P, et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am*. 2013;95(20):1885-6. doi: 10.2106/00004623-201310160-00010. [PubMed: 24288804].
- Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, et al. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(3):436-49. doi: 10.1007/s00167-011-1713-8. [PubMed: 22037809].
- Neustadt DH. Intra-articular injections for osteoarthritis of the knee. *Cleve Clin J Med*. 2006;73(10):897-8-906-11. doi: 10.3949/ccjm.73.10.897. [PubMed: 17044315].
- Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006;(2). CD005328. doi: 10.1002/14651858.CD005328.pub2. [PubMed: 16625636].
- Hochberg M, Altman R, Toupin K. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43(9):1905-15. doi: 10.1002/1529-0131(200009)43:9<1905::AID-ANR1>3.0.CO;2-P. [PubMed: 11014340].
- Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop*. 2014;5(3):351-61. doi: 10.5312/wjo.v5.i3.351. [PubMed: 25035839]. [PubMed Central: PMC4095029].
- Trueba Davaillo CA, Trueba Vasavilbaso C, Navarrete Alvarez JM, Coronel Granado P, Garcia Jimenez OA, Gimeno Del Sol M, et al. Clinical efficacy of intra-articular injections in knee osteoarthritis: a prospective randomized study comparing hyaluronic acid and betamethasone. *Open Access Rheumatol*. 2015;7:9-18. doi: 10.2147/OARRR.S74553. [PubMed: 27790040]. [PubMed Central: PMC5045121].
- Garg N, Perry L, Deodhar A. Intra-articular and soft tissue injections, a systematic review of relative efficacy of various corticosteroids. *Clin Rheumatol*. 2014;33(12):1695-706. doi: 10.1007/s10067-014-2572-8. [PubMed: 24651914].
- Douglas RJ. Corticosteroid injection into the osteoarthritic knee: drug selection, dose, and injection frequency. *Int J Clin Pract*. 2012;66(7):699-704. doi: 10.1111/j.1742-1241.2012.02963.x. [PubMed: 22698422].
- Iannone F, Lapadula G. Obesity and inflammation—targets for OA therapy. *Curr Drug Targets*. 2010;11(5):586-98. doi: 10.2174/138945010791011857. [PubMed: 20199391].
- 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*. 2016;32(3):495-505. doi: 10.1016/j.arthro.2015.08.005. [PubMed: 26432430].
- Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. *Curr Rev Musculoskelet Med*. 2008;1(3-4):165-74. doi: 10.1007/s12178-008-9032-5. [PubMed: 19468902]. [PubMed Central: PMC2682411].
- 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):657-72. doi: 10.1136/bjsports-2014-094036. [PubMed: 25416198].
- Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2017;12(1):16. doi: 10.1186/s13018-017-0521-3. [PubMed: 28115016]. [PubMed Central: PMC5260061].
- Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):472-9. doi: 10.1007/s00167-009-0940-8. [PubMed: 1983876].
- Tehrani A, Esfehiani-Mehr B, Pirjani R, Rezaei N, Sadat Heidary S, Sepidarkish M. Application of Autologous Platelet-Rich Plasma (PRP) on Wound Healing After Caesarean Section in High-Risk Patients. *Iran Red Crescent Med J*. 2016;18(7):e34449. doi: 10.5812/ircmj.34449. [PubMed: 27660723]. [PubMed Central: PMC5027131].
- Ilhanli I, Guder N, Gul M. Platelet-Rich Plasma Treatment With Physical Therapy in Chronic Partial Supraspinatus Tears. *Iran Red Crescent Med J*. 2015;17(9):e23732. doi: 10.5812/ircmj.23732. [PubMed: 26473076]. [PubMed Central: PMC4601247].
- Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, 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):1575-82. doi: 10.1177/0363546515582027. [PubMed: 25952818].
- Hashemi M, Nabi BN, Saberi A, Sedighinejad A, Haghighi M, Farzi F. The comparison between two methods for the relief of knee osteoarthritis pain: Radiofrequency and intra-periarticular ozone injection: A clinical trial study. *Int J Med Res Health Sci*. 2016;5(7s):539-46.

32. 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):901-8. [PubMed: 26173792].
33. Joshi Jubert N, Rodriguez L, Reverte-Vinaixa MM, Navarro A. Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. *Orthop J Sports Med*. 2017;5(2):2.3259671166894E+15. doi: 10.1177/2325967116689386. [PubMed: 28255569]. [PubMed Central: PMC5315239].
34. Chan K, Ngai H, Ip K, Lam K, Lai W. Co-morbidities of patients with knee osteoarthritis. *Hong Kong Med J*. 2009;15(3):168-74.
35. Kijowski R, Blankenbaker D, Stanton P, Fine J, De Smet A. Arthroscopic validation of radiographic grading scales of osteoarthritis of the tibiofemoral joint. *AJR Am J Roentgenol*. 2006;187(3):794-9. doi: 10.2214/AJR.05.1123. [PubMed: 16928947].
36. Salavati M, Mazaheri M, Negahban H, Sohani SM, Ebrahimian MR, Ebrahimi I, et al. Validation of a Persian-version of Knee injury and Osteoarthritis Outcome Score (KOOS) in Iranians with knee injuries. *Osteoarthritis Cartilage*. 2008;16(10):1178-82. doi: 10.1016/j.joca.2008.03.004. [PubMed: 18411065].
37. Hassan AS, El-Shafey AM, Ahmed HS, Hamed MS. Effectiveness of the intra-articular injection of platelet rich plasma in the treatment of patients with primary knee osteoarthritis. *Egypt Rheumatol*. 2015;37(3):119-24. doi: 10.1016/j.ejr.2014.11.004.
38. Kilincoglu V, Yeter A, Servet E, Kangal M, Yildirim M. Short term results comparison of intraarticular platelet-rich plasma (prp) and hyaluronic acid (ha) applications in early stage of knee osteoarthritis. *Int J Clin Exp Med*. 2015;8(10):18807-12. [PubMed: 26770499]. [PubMed Central: PMC4694399].
39. 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):278-83. [PubMed: 24119476].
40. Raynauld JP, Buckland-Wright C, Ward R, Choquette D, Haraoui B, Martel-Pelletier J, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2003;48(2):370-7. doi: 10.1002/art.10777. [PubMed: 12571845].