

# Adding Intra-Articular Growth Hormone to Platelet Rich Plasma under Ultrasound Guidance in Knee Osteoarthritis: A Comparative Double-Blind Clinical Trial

Poupak Rahimzadeh,<sup>1</sup> Farnad Imani,<sup>1\*</sup> Seyed-Hamid-Reza Faiz,<sup>1</sup> Mahmoud-Reza Alebouyeh,<sup>2</sup> Damoon

Azad-Ehyaeei,<sup>2</sup> Leila Bahari,<sup>2</sup> Arash Memarian,<sup>2</sup> and Kyung-Hoon Kim<sup>3</sup>

<sup>1</sup>Pain Research Center, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Anesthesiology, Iran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Department of Anesthesiology and Pain Medicine, Pusan National University, Korea

\*Corresponding author: Farnad Imani, Pain Research Center, Rasoul Akram Medical Center, Iran University of Medical Sciences, Tehran, Iran. Tel: +98-2166515758, E-mail: farnadimani@yahoo.com

Received 2016 August 30; Revised 2016 September 26; Accepted 2016 October 15.

## Abstract

**Introduction:** Intra-articular injections of platelet rich plasma (PRP) for the treatment of knee osteoarthritis have been shown to reduce pain and improve joint function. The aim of this study is to examine the joint function by adding intra-articular growth hormone to platelet rich plasma. This study was performed on the individuals with knee osteoarthritis and under ultrasound guidance.

**Methods:** Fifty four patients who were scheduled for ultra-sound guided intra-articular injection were enrolled in the study. The patients were randomly allocated to groups P (platelet rich plasma) and PS (platelet rich plasma and Somatropin). Group P and PS were injected with 5 mL of platelet rich plasma, and 4 IU growth hormone (Somatropin) added to platelet rich plasma, respectively. Intra-articular injection was performed in two steps; the onset of study and one month after. Knee joint function based on Western Ontario and McMaster osteoarthritis index (WOMAC) score at the baseline, 1 and 2 month later, and complications were evaluated.

**Results:** WOMAC score in both groups has been significantly reduced after injections ( $P = 0.030$ ). WOMAC score reduction in group PS in first month was significantly higher than group P, but in second month 2, the difference between two groups was not significant ( $P = 0.235$ ). No complication was observed.

**Conclusions:** These results showed that adding growth hormone to platelet rich plasma for intra-articular injection improved function of the osteoarthritic knee joint in short period of time.

**Keywords:** Growth Hormone, Intra-Articular Injection, Platelet-Rich Plasma, Ultrasound

## 1. Introduction

Knee osteoarthritis, as a progressive disease is one of the most common causes of pain, motor disorder and disability in the elderly (1-3). Non-surgical interventions for pain control of knee osteoarthritis include weight loss, exercise, changes in daily activities, physiotherapy, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics and intra-articular injection such as corticosteroids, hyaluronic acid, Growth hormone, dextrose and performing pulsed radiofrequency (4-9). Corticosteroids and NSAIDs are common medical treatments. However, the higher risk of gastrointestinal bleeding is a common systemic side effect of NSAIDs. Furthermore, intra-articular corticosteroid injection causes damage to the articular cartilage, higher incidence of secondary infection and other side effects which limit its consumption (10).

By increasing age, the cartilage is eroded and endures degenerative changes due to physiological and biome-

chanical changes as well as metabolic effects and trauma (11). The ability of cartilage in regenerating itself is limited due to restriction of vessel perfusion and innervation and less systemic adjustment after degeneration. Therefore, intra-articular injection of drugs or drug combination with the restructuring abilities in cartilage tissue repair has always been the focus of this field (12). Various compounds such as hyaluronic acid, and irritants such as dextrose and erythropoietin have been used so far with various effectiveness levels and mechanisms (8, 13). Growth hormone has generative and constructive effect on cartilage and chondrocyte (9). The concentration of platelets in platelet-rich plasma (PRP) is above the baseline value (14). Platelets are sources with high concentrations of cytokines and a group of growth factors regulating the repair process including the regeneration of tissues (15). It seems that certain growth factors in PRP such as  $\beta$ -Transforming growth factor are associated with chondrogenesis in cartilage repair (16).

In addition, growth hormone leaves regulatory effects in skeletal growth and bone mineral density. This hormone also stimulates the growth of cartilage through the local and systemic production of Insulin like Growth factor-I(IGF-I) and possibly by direct stimulation of chondrocyte proliferation (9, 17).

According to these facts, this study intended to examine the knee joint function by adding growth hormone to PRP in the intra-articular injectate solution.

## 2. Materials and Methods

In this clinical, randomized, double-blind trial, a total of 54 patients with knee osteoarthritis were enrolled who were candidate for the intra-articular injection. The subjects were included in the study after submitting their written consent. The inclusion criteria were age 40 - 70 years old, stage I or II of knee osteoarthritis (by Kellgren and Lawrence scale, Table 1). The exclusion criteria were rheumatoid arthritis, hemophilia, history of previous knee surgery, drug addiction, alcohol and use of anti-coagulants and NSAIDs in the past seven days. This trial was registered with IRCT2015070210599N4.

The preliminary information of the patients including gender, weight, height and age were recorded.

According to the study by Gobbi et al., the activity scores of patients with knee osteoarthritis before and 6 months after injection of PRP were  $77.8 \pm 5.7$  and  $86.3 \pm 4.7$ , respectively. Given the confidence level of 0.05 and power of 95%, the sample size was estimated to be 21 (18). However, the sample size in the present study was expanded to 27 subjects. Then, the patients were divided randomly into two equal groups of 27. Initially, the patient's knee involvement was measured based on WOMAC scale. WOMAC is composed of the following three components: 1) Pain (5 items), 2) Joint stiffness (2 items), and 3) Knee function (17 items). Scoring in each case ranged from 0 to 4, and the total score of the scale cover 0 to 96 (19). After preparing routine cardiac monitoring (blood pressure, heart rate, and ECG) and blood oxygen saturation, 20ml of patient's blood was taken intravenously under sterile conditions and placed in the centrifuge kits (Becton Dickinson, UK) for PRP preparation. This solution was centrifuged at 3200 rpm for 20 minutes. The plasma at the top of the solution was isolated and again centrifuged for 5 minutes more at 1500 rpm. Then, 5 mL of plasma at the top of this solution was prepared for intra-articular injection in group P. In group PS, 4 units of growth hormone (Somatropin, Bio Sidus, Argentina) were added to the solution of PRP.

The intra-articular injection was performed as follows: under sterile conditions and, after local anesthesia and putting the multi-frequency linear probe (6 - 13 MHz with

6 cm penetration) placed at the top of the patella horizontally. Sono-visible needle 22 gauge with 50 mm length (Visioplex Needle, Vygon, France) from superolateral quadrant of the patella entered and directed with in-plane technique under ultrasound guidance (SonoSite, S-Nerve) into the knee joint space. Then, the prepared solution was injected into the knee joints without the patients and the physician being aware of the difference between the contents of the syringes. For an hour, the patients were monitored and then discharged in case there were not any adverse effects. In addition, the same procedure was repeated one month later in both groups.

The condition of patient's knee at baseline (immediately before the first injection), one month later (immediately before the second injection), and two months later (one month after the second injection) were assessed through WOMAC questionnaire, as well as the incidence of any side effects. The data were analyzed through SPSS 20. Chi-square test was used for the qualitative data. The independent t-test was used to compare the quantitative data. To assess the quantitative data in multiple times, the analysis of variance with repeated observations was used. The P values less than 0.05 were considered significant. The Lambda Wilks and Mauchly tests were used to compare differences between groups at different times.

## 3. Results

In this study, 54 patients with knee osteoarthritis were evaluated. Table 2 displays the demographic variables.

The mean of WOMAC at baseline (immediately before the first injection) was  $66.67 \pm 9.23$  in P group and  $64.33 \pm 10.69$  in PS group ( $P = 0.460$ ).

The mean of WOMAC one month later (just before the second injection), was  $46.67 \pm 11.53$  in group P and  $40.00 \pm 17.29$  in group PS. Data were analyzed through the independent t-test, indicating that WOMAC in group PS was significantly lower than in group P ( $P = 0.030$ ).

The mean of WOMAC two months later (one month after the second injection) was  $34.62 \pm 13.79$  in group P and  $29.60 \pm 18.58$  in group PS. The difference between the two groups was not significant ( $P = 0.235$ ).

The variance test with repeated measure analysis was used to assess the WOMAC scores in the two groups at different times. Moreover, the Mauchly and Wilks Lambda tests were used to compare differences between the groups. The intergroup analysis using the Wilks Lambda test demonstrated that the mean variations of WOMAC decreased significantly in both groups ( $F = 128, O = 0.0001$ ). Due to the significance of Mauchly test ( $P = 0.008$ ), the Greenhouse-Geisser test was employed to assess the difference between the two groups. The test showed that the

**Table 1.** Kellgren- Lawrence Scale

Degree	Definition
0	No radiographic features of osteoarthritis
1	Possible joint space narrowing and osteophytes formation
2	Definite osteophyte formation with possible joint space narrowing
3	Multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity
4	Large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity

**Table 2.** Demographic Variables of the Patients under Study

	MALE, No. (%)	Female, No. (%)	Age, Mean $\pm$ SD	BMI, Kg/m <sup>2</sup> , Mean $\pm$ SD
Group P	15 (55.6)	12 (44.4)	63.67 $\pm$ 9.64	28.2 $\pm$ 3.6
Group PS	13 (48.2)	14 (51.8)	61.26 $\pm$ 9.48	29.6 $\pm$ 4.2
P value	0.586 <sup>a</sup>	0.907 <sup>a</sup>	0.197 <sup>a</sup>	

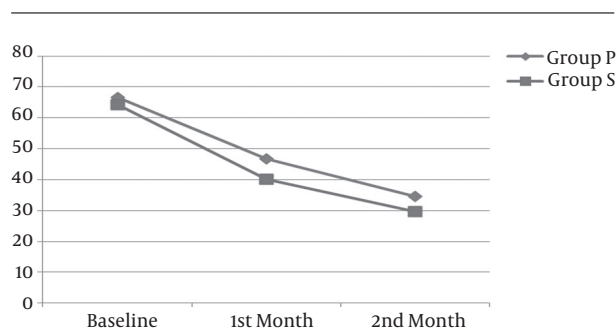
<sup>a</sup>There is no significant difference.

**Table 3.** WOMAC Scores at the Assessed Times

	Group P, Mean $\pm$ SD	Group PS, Mean $\pm$ SD	P Value
Baseline (immediately before the first injection)	66.67 $\pm$ 9.23	64.33 $\pm$ 10.69	0.460
1st month (one month after the first injection)	46.67 $\pm$ 11.53	40.00 $\pm$ 17.29	0.030 <sup>a</sup>
2nd month (one month after the second injection)	34.62 $\pm$ 13.79	29.60 $\pm$ 18.58	0.235

<sup>a</sup>The difference is significant.

two groups were not significantly different despite a further decline in the WOMAC for group PS at the end of the second month ( $F = 0.703$ ,  $P = 0.476$ ).

**Figure 1.** WOMAC Values at the Three Spans

#### 4. Discussion

The results of this study showed that the addition of growth hormone to PRP through intra-articular injection in the knee joint of patients with knee osteoarthritis

caused lower WOMAC scores in the first month. In addition, the WOMAC score at the end of the second month declined, even though it was not significantly different.

There have been a variety of non-invasive and semi-invasive methods used in the treatment of knee osteoarthritis. These treatments include physical therapy, nonsteroidal anti-inflammatory drugs, glucosamine, corticosteroid injections, hyaluronic acid, PRP, prolotherapy, radiofrequency, and the use of growth hormone (12). Intra-articular opioids have been used more for acute pain setting (20). There are several studies that evaluated the effects of PRP to alleviate the symptoms and the pain caused by osteoarthritis (16, 17, 19). The activated platelets release mediators such as growth factors and cytokines. In vivo studies, the PRP may increase chondrocyte proliferation and differentiation. The PRP is likely to have anti-inflammatory effects, which may exert this effect by inhibiting the NF-KB pathway (21).

In a study on animal model (pig), Lippross found that the intra-articular injection of PRP could significantly reduce joint inflammation (22).

In a study by Kanchanatawan et al., the short-term out-

**Table 4.** Mean Values of WOMAC by its Components of Pain, Joint Stiffness and Physical Function

Groups	Baseline	First Month	Second Month	P Value
<b>Group P</b>				
<b>Pain</b>	14.33 ± 2.23	9.80 ± 1.96	7.61 ± 2.1	0.0001
<b>Stiffness</b>	3.66 ± 1.98	2.80 ± 1.11	1.62 ± 0.84	0.0001
<b>Physical function</b>	48.68 ± 7.54	34.07 ± 8.92	20.37 ± 9.11	0.0001
<b>Total</b>	66.67 ± 9.23	46.67 ± 11.2	34.62 ± 13.79	
<b>Group PS</b>				
<b>Pain</b>	14.7 ± 2.45	8.4 ± 1.84	5.92 ± 1.78	0.0001
<b>Stiffness</b>	3.85 ± 1.74	2.28 ± 1.56	1.56 ± 0.84	0.0001
<b>Physical function</b>	48.35 ± 8.41	29.32 ± 9.76	22.12 ± 11.55	0.0001
<b>Total</b>	64.33 ± 10.69	40.00 ± 17.29	29.60 ± 18.58	

comes of intra-articular injection of PRP in the treatment of knee osteoarthritis were evaluated (23). The results of that study showed that the short-term outcomes (less than one year) from the injection of PRP improved the performance of patients (including the WOMAC) compared with hyaluronic acid and placebo. The researcher argued that intra-articular injection of PRP was generally more effective than hyaluronic acid and placebo in reducing the symptoms and improving the quality of life.

In a study released by Angoorani et al., the intra-articular injection of PRP was compared by stimulating intradermal nerves (24). The results showed that intra-articular injection of PRP provided an effective and safe technique for short-term treatment of patients with knee osteoarthritis. In another study, Forogh et al. examined the effect of a single dose injection of PRP and corticosteroid on knee osteoarthritis (25). The results of this study showed that a single dose of PRP injection reduced the joint pain to a greater extent and longer than corticosteroids. Moreover, it relieved the symptoms and enhanced the daily activity and quality of life in the short term. In this study, the patients' pain and osteoarthritis outcomes were measured through the visual analogue scale (VAS). The patients were evaluated in the second and sixth months after injection. However, our study rather involved WOMAC which is a more comprehensive scale and the patients received two injections, each time evaluated one month after injection.

In another systematic review conducted by Campbell et al., the intra-articular PRP was compared against corticosteroids, hyaluronic acid, oral NSAIDs and placebo (26). The results showed that intra-articular injection of PRP could provide a therapy for knee osteoarthritis with the potential to relieve symptoms even for 12 months. However, the frequent use of PRP injection increases the risk of ad-

verse reactions (25). In one study, a single dose injection of PRP and its dual injection led to a significant difference in comparison with saline injection (19). In this study, both pain and physical activities similar to the current study were assessed through WOMAC at 1.5, 3 and 6 months after injection. Vaquerizo et al. found that there was a significant difference between the PRP and hyaluronic acid groups, considering 50% reduction in WOMAC scores and the PRP group experienced higher improvement in joint function (27).

Growth hormone is known as an important regulator of bone growth and bone mineral density. This factor stimulates the cartilage growth probably by producing local and systemic IGF-1 as well as by direct stimulation of cartilage cell proliferation. Circulating growth hormone or one of its mediators may be responsible for osteochondral defect repair (28).

This study explored the addition of growth hormone to PRP combined in order to reduce the symptoms of knee osteoarthritis. Compared with only PRP, this combination managed to significantly relieve pain and joint stiffness, thus improving the performance of the patients at the end of the first month after the injection. Although this difference was not significant at the end of the second month, the average pain, joint stiffness and impaired function was to a large extent lower in Group PS than the other group.

Fortier et al. examined the role of growth hormone in cartilage repair as a review study (29). This study showed that the use of growth factors was promising in the treatment of localized cartilage defects such as osteoarthritis. Nonetheless, there is still a need for further studies in this area. The results of a study by Ekenstedt et al. suggested that the chronic lack of growth hormone causes further destruction in the articular cartilage in osteoarthritis (30). In an animal study by Kim et al., it was found that the si-

multaneous injection of hyaluronic acid and growth hormone improves the osteoarthritis more effectively than hyaluronic acid alone (9).

There were a few limitations in the current study, including the limited follow-up time. It is recommended that future studies should evaluate patients for a longer period.

#### 4.1. Conclusions

The use of platelet-rich plasma along with growth hormone may improve knee function in patients with osteoarthritis such as pain, joint stiffness and effective performance of activities.

#### References

- Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage*. 2011;**19**(5):478–82. doi: [10.1016/j.joca.2010.09.013](https://doi.org/10.1016/j.joca.2010.09.013). [PubMed: [21396464](https://pubmed.ncbi.nlm.nih.gov/21396464/)].
- Suri P, Morgenroth DC, Hunter DJ. Epidemiology of osteoarthritis and associated comorbidities. *PM R*. 2012;**4**(5 Suppl):S10–9. doi: [10.1016/j.pmrj.2012.01.007](https://doi.org/10.1016/j.pmrj.2012.01.007). [PubMed: [22632687](https://pubmed.ncbi.nlm.nih.gov/22632687/)].
- Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol*. 2006;**20**(1):3–25. doi: [10.1016/j.berh.2005.09.007](https://doi.org/10.1016/j.berh.2005.09.007). [PubMed: [16483904](https://pubmed.ncbi.nlm.nih.gov/16483904/)].
- Imani F, Rahimzadeh P. Interventional pain management according to evidence-based medicine. *Anesth Pain Med*. 2012;**1**(4):235–6. doi: [10.5812/aapm.4514](https://doi.org/10.5812/aapm.4514). [PubMed: [24904805](https://pubmed.ncbi.nlm.nih.gov/24904805/)].
- Imani F. Using pulsed radiofrequency for chronic pain. *Anesth Pain Med*. 2012;**1**(3):155–6. doi: [10.5812/kowsar.22287523.4047](https://doi.org/10.5812/kowsar.22287523.4047). [PubMed: [24904784](https://pubmed.ncbi.nlm.nih.gov/24904784/)].
- Schianchi PM, Sluijter ME, Balogh SE. The Treatment of Joint Pain with Intra-articular Pulsed Radiofrequency. *Anesth Pain Med*. 2013;**2**(2):250–5. doi: [10.5812/aapm.10259](https://doi.org/10.5812/aapm.10259). [PubMed: [24282777](https://pubmed.ncbi.nlm.nih.gov/24282777/)].
- Sluijter ME, Imani F. Evolution and mode of action of pulsed radiofrequency. *Anesth Pain Med*. 2013;**2**(4):339–41. doi: [10.5812/aapm.10213](https://doi.org/10.5812/aapm.10213). [PubMed: [24223349](https://pubmed.ncbi.nlm.nih.gov/24223349/)].
- Rahimzadeh P, Imani F, Faiz SH, Entezary SR, Nasiri AA, Ziaefard M. Investigation the efficacy of intra-articular prolotherapy with erythropoietin and dextrose and intra-articular pulsed radiofrequency on pain level reduction and range of motion improvement in primary osteoarthritis of knee. *J Res Med Sci*. 2014;**19**(8):696–702. [PubMed: [25422652](https://pubmed.ncbi.nlm.nih.gov/25422652/)].
- Kim SB, Kwon DR, Kwak H, Shin YB, Han HJ, Lee JH, et al. Additive effects of intra-articular injection of growth hormone and hyaluronic acid in rabbit model of collagenase-induced osteoarthritis. *J Korean Med Sci*. 2010;**25**(5):776–80. doi: [10.3346/jkms.2010.25.5.776](https://doi.org/10.3346/jkms.2010.25.5.776). [PubMed: [20436717](https://pubmed.ncbi.nlm.nih.gov/20436717/)].
- Smelter E, Hochberg MC. New treatments for osteoarthritis. *Curr Opin Rheumatol*. 2013;**25**(3):310–6. doi: [10.1097/BOR.0b013e32835f69b4](https://doi.org/10.1097/BOR.0b013e32835f69b4). [PubMed: [23425965](https://pubmed.ncbi.nlm.nih.gov/23425965/)].
- Howell R, Kumar NS, Patel N, Tom J. Degenerative meniscus: Pathogenesis, diagnosis, and treatment options. *World J Orthop*. 2014;**5**(5):597–602. doi: [10.5312/wjo.v5.i5.597](https://doi.org/10.5312/wjo.v5.i5.597). [PubMed: [25405088](https://pubmed.ncbi.nlm.nih.gov/25405088/)].
- Kon E, Filardo G, Drobic M, Madry H, Jelic M, van Dijk N, et al. Non-surgical management of early knee osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2011;**20**(3):436–49. doi: [10.1007/s00167-011-1713-8](https://doi.org/10.1007/s00167-011-1713-8).
- Xing D, Wang B, Liu Q, Ke Y, Xu Y, Li Z, et al. Intra-articular Hyaluronic Acid in Treating Knee Osteoarthritis: a PRISMA-Compliant Systematic Review of Overlapping Meta-analysis. *Sci Rep*. 2016;**6**:32790. doi: [10.1038/srep32790](https://doi.org/10.1038/srep32790). [PubMed: [27616273](https://pubmed.ncbi.nlm.nih.gov/27616273/)].
- Pietrzak WS, Eppley BL. Platelet Rich Plasma: Biology and New Technology. *J Craniofacial Surgery*. 2005;**16**(6):1043–54. doi: [10.1097/01.scs.0000186454.07097.bf](https://doi.org/10.1097/01.scs.0000186454.07097.bf).
- Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev*. 2003;**83**(3):835–70. doi: [10.1152/physrev.00031.2002](https://doi.org/10.1152/physrev.00031.2002). [PubMed: [12843410](https://pubmed.ncbi.nlm.nih.gov/12843410/)].
- 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](https://doi.org/10.1007/s12178-008-9032-5). [PubMed: [19468902](https://pubmed.ncbi.nlm.nih.gov/19468902/)].
- Nemirovskiy O, Zheng YJ, Tung D, Korniski B, Settle S, Skepner A, et al. Pharmacokinetic/pharmacodynamic (PK/PD) differentiation of native and PEGylated recombinant human growth hormone (rhGH and PEG-rhGH) in the rat model of osteoarthritis. *Xenobiotica*. 2010;**40**(8):586–92. doi: [10.3109/00498254.2010.488303](https://doi.org/10.3109/00498254.2010.488303). [PubMed: [20509748](https://pubmed.ncbi.nlm.nih.gov/20509748/)].
- Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. *Sports Health*. 2012;**4**(2):162–72. doi: [10.1177/1941738111431801](https://doi.org/10.1177/1941738111431801). [PubMed: [23016084](https://pubmed.ncbi.nlm.nih.gov/23016084/)].
- Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;**41**(2):356–64. doi: [10.1177/0363546512471299](https://doi.org/10.1177/0363546512471299). [PubMed: [23299850](https://pubmed.ncbi.nlm.nih.gov/23299850/)].
- Imani F, Entezary S, Razi M, Jafarian AA, Yousefshahi F, Etemadi H, et al. The effect of intra-articular meperidine and bupivacaine 0.5% on postoperative pain of arthroscopic knee surgery; a randomized double blind clinical trial. *Anesth Pain Med*. 2015;**5**(1):27470. doi: [10.5812/aapm.27470](https://doi.org/10.5812/aapm.27470). [PubMed: [25830119](https://pubmed.ncbi.nlm.nih.gov/25830119/)].
- Lai LP, Stitik TP, Foye PM, Georgy JS, Patibanda V, Chen B. Use of Platelet-Rich Plasma in Intra-Articular Knee Injections for Osteoarthritis: A Systematic Review. *PM R*. 2015;**7**(6):637–48. doi: [10.1016/j.pmrj.2015.02.003](https://doi.org/10.1016/j.pmrj.2015.02.003). [PubMed: [25687110](https://pubmed.ncbi.nlm.nih.gov/25687110/)].
- Lippross S, Moeller B, Haas H, Tohidnezhad M, Steubesand N, Wruck CJ, et al. Intraarticular injection of platelet-rich plasma reduces inflammation in a pig model of rheumatoid arthritis of the knee joint. *Arthritis Rheum*. 2011;**63**(11):3344–53. doi: [10.1002/art.30547](https://doi.org/10.1002/art.30547). [PubMed: [21769848](https://pubmed.ncbi.nlm.nih.gov/21769848/)].
- 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*. 2016;**24**(5):1665–77. doi: [10.1007/s00167-015-3784-4](https://doi.org/10.1007/s00167-015-3784-4). [PubMed: [26387122](https://pubmed.ncbi.nlm.nih.gov/26387122/)].
- 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. [PubMed: [26478881](https://pubmed.ncbi.nlm.nih.gov/26478881/)].
- Foroogh 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](https://pubmed.ncbi.nlm.nih.gov/26173792/)].
- Campbell KA, Saltzman BM, Mascarenhas R, Khair MM, Verma NN, Bach BJ, et al. Does Intra-articular Platelet-Rich Plasma Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses. *Arthroscopy*. 2015;**31**(11):2213–21. doi: [10.1016/j.arthro.2015.03.041](https://doi.org/10.1016/j.arthro.2015.03.041). [PubMed: [26033459](https://pubmed.ncbi.nlm.nih.gov/26033459/)].
- Vaquerizo V, Plasencia MA, Arribas I, Seijas R, Padilla S, Orive G, 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*. 2013;**29**(10):1635-43. doi: [10.1016/j.arthro.2013.07.264](https://doi.org/10.1016/j.arthro.2013.07.264). [PubMed: [24075613](https://pubmed.ncbi.nlm.nih.gov/24075613/)].
28. Adams ME, Atkinson MH, Lussier AJ, Schulz JJ, Siminovitch KA, Wade JP, et al. The role of viscosupplementation 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 and Cartilage*. 1995;**3**(4):213-25. doi: [10.1016/s1063-4584\(05\)80013-5](https://doi.org/10.1016/s1063-4584(05)80013-5).
29. Fortier LA, Mohammed HO, Lust G, Nixon AJ. Insulin-like growth factor-I enhances cell-based repair of articular cartilage. *J Bone Joint Surg Br*. 2002;**84**(2):276-88. [PubMed: [11922373](https://pubmed.ncbi.nlm.nih.gov/11922373/)].
30. Ekenstedt KJ, Sonntag WE, Loeser RF, Lindgren BR, Carlson CS. Effects of chronic growth hormone and insulin-like growth factor 1 deficiency on osteoarthritis severity in rat knee joints. *Arthritis Rheum*. 2006;**54**(12):3850-8. doi: [10.1002/art.22254](https://doi.org/10.1002/art.22254). [PubMed: [17133593](https://pubmed.ncbi.nlm.nih.gov/17133593/)].