Journal of Arthroscopy and Joint Surgery 4 (2017) 65–71

Contents lists available at ScienceDirect

Journal of Arthroscopy and Joint Surgery

journal homepage: www.elsevier.com/locate/jajs

Research paper

A study assessing intra-articular PRP vs PRP with HMW HA vs PRP with LMW HA in early knee osteoarthritis

G. Jacob*, V. Shetty, S. Shetty

Department of Orthopedics KS Hegde Hospital Mangalore, India

ARTICLE INFO

Article history:
Received 7 November 2016
Accepted 9 August 2017
Available online 14 August 2017

Keywords:
Osteoarthritis
Platelet rich plasma
Hyaluronic Acid

ABSTRACT

Objective: We aim to study the effects of platelet rich plasma (PRP) and hyaluronic acid injections in treatment of early Osteoarthritis (OA). We assess which form of HA is most beneficial and whether combining PRP and HA have a better clinical outcome.
Design: Data: Cases diagnosed with early knee OA in the department of Orthopedic's, K. S. Hegde Medical Academy.
Sample Size: Total 51 patients divided into 3 groups

- Group 1: PRP group
- Group 2: PRP with LMW HA
- Group 3: PRP with HMW HA

Inclusion criteria
- Pain or swelling of knee >4 months
- Kellgren Lawrence 0-III on X-ray

Exclusion criteria
- Kellgren-Lawrence >grade 3
- Rheumatoid arthritis
- Haematological diseases
- Severe cardiovascular diseases
- Infections
- Diabetes Mellitus
- Patients in therapy with anticoagulants or anti aggregants

Study Method: Patients selected based on inclusion criteria and using block randomisation divided into a group. Pre injection visual analogue score (VAS) and International knee documentation committee score (IKDC) proforma are done. The decided injection is then performed and the patient followed up at 6 weeks and 6 months.
Statistics: Paired T test
One way Anova and Posthoc test
$P = 0.05$ significant
Results: All groups showed statistically significant decrease in VAS score and increase in IKDC scores with $P < 0.05$. LMW+ PRP injection showed the greatest difference in IKDC and VAS scores though this difference was not statistically significant.

* Corresponding author.
E-mail address: drgeorge.jac@gmail.com (G. Jacob).

http://dx.doi.org/10.1016/j.jajs.2017.08.008

Conclusion: All injections are a beneficial form of treatment. LMW HA + PRP is the most beneficial injection all though not statistically significant.

1. Introduction

Osteoarthrosis (OA) is the most common disease of joints in adults around the world. Felson et al. reported that about one-third of all adults have radiological signs of osteoarthritis.[1] It is a clinical syndrome of joint pain characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and inflammation of the joint.

Tackling the progression of the disease and attenuating the degradation of cartilage and joint health has been a major dilemma in the field of orthopedics. Many methods and treatment have been proposed in order to avoid the total knee arthroplasty. Non-steroidal anti-inflammatory drugs (NSAIDS) have been essential in treatment and highly effective in pain control but do not play any role in addressing the joint health.

Exercise and physiotherapy have been in wide agreement as adjuvant in treatment. Reduction of weight is paramount and it is well understood that the cartilage in the joint is under more insult with higher body mass indexes. Off loading braces to reduce axial forces acting on the more worn side of the joint and even tibial osteotomies to re align the entire lower limb and weight transmission have been advocated. Nutracueticals such as chondroitin and glucosamine have been employed but are not widely accepted to have any role in prevention or effects of the disease.

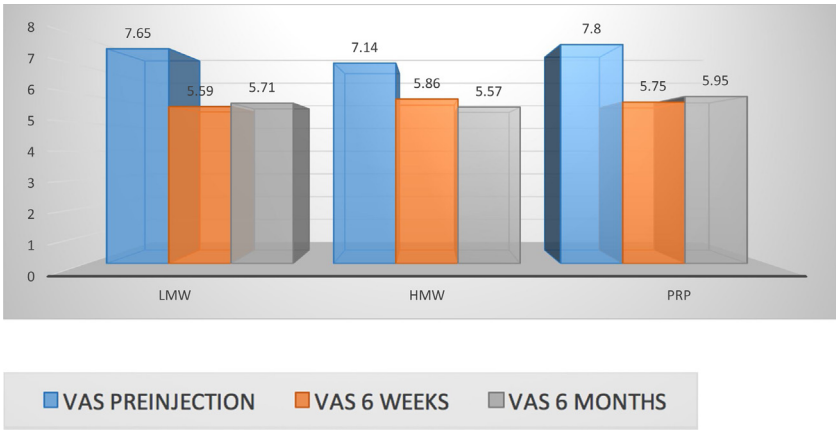
Platelet rich plasma (PRP) is a sample of autologous blood, which has been prepared to have a high concentration of platelets, associated growth factors and cytokines. PRP use was first published by Marx et al, a maxillofacial surgeon who used it to fill cancellous mandibular defects.[2] The uses of PRP since have been many showing promising results in some fields and less so in others. The general idea being that it contains the necessary recipe of ingredients to stimulate repair and to some extent regeneration.

Hyaluronic acid (HA) is a glycosaminoglycan that is found throughout the connective, epithelial and neural tissue in the body. It is postulated to be an integral part of synovial fluid in that it not only stimulates cell proliferation and migration, but also serves as a lubricant to the joint propagation. [3] Osteoarthrosis is associated with a reduced amount of hyaluronic acid within the joint. Many different forms of the molecule have been derived varying in primary source to molecular weight and more recently combined with other drugs such as chondroitin and sorbitol.

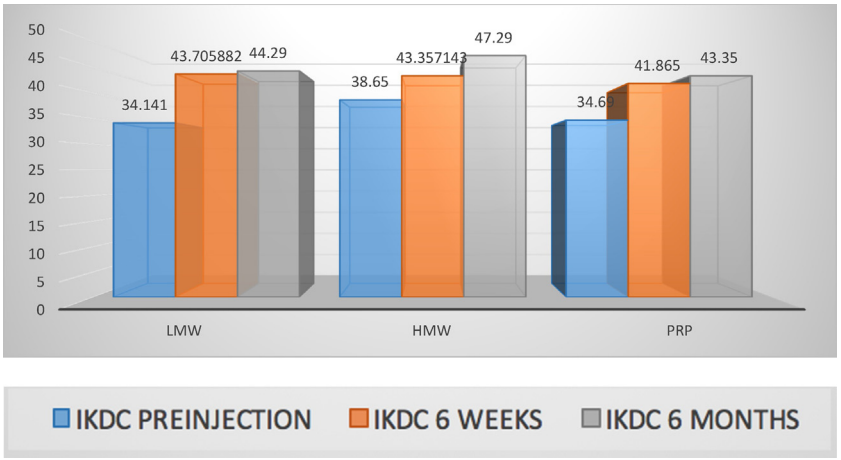
PRP has been used in orthopedics for almost two decades now showing varying outcomes and results. The purpose of the study is to determine whether PRP and viscosupplementation have any role in the treatment of early osteoarthritis of the knee joint. For this purpose, three groups; PRP, PRP + Low molecular weight (LMW) HA, PRP + High molecular weight (HMW) HA have been made. Subjective and functional scores pre and post injection will shed light on the effect this modality of treatment has on the disease and which group of injection is the most efficacious treatment. Joint replacement addresses final stages of the condition but earlier less symptomatic knees in early stages of the condition and do not warrant surgery need better effective treatment options. We aim to evaluate platelet rich plasma and visco-supplementation as a viable treatment option for early joint osteoarthritis of the knee joint.

2. Materials and methods

- Study type-comparative study
- Source- All the patients with early osteoarthritis of the knee joint, presenting to the Department of Orthopaedics K. S. Hegde Charitable hospital from February 2014 to February 2016 were included in the study after explaining the procedure and getting their consent.
- Consent: Institutional ethical committee clearance and patient consent
- Methodology: a patient has been diagnosed with early OA knee, he or she was added to one of three groups randomly.
  - Group 1: PRP group (20 patients)
  - Group 2: PRP with LMW HA (17 patients)
  - Group 3: PRP with HMW HA (14 patients)
- Inclusion criteria



Graph 1. VAS pre injection Vas 6 weeks and Vas 6 months.



Graph 2. Intra group International Knee Documentation Committee Score comparison.

Table 1
Intragroup Comparison paired T test Platelet rich plasma.

PRP		Mean	N	Std. Deviation	Paired Differences		t	df	P VALUE
					Mean Difference	Std. Deviation			
Pair 1	IKDC PREINJECTION	34.69	20	10.11	−7.18	4.97	-6.45	19	<**0.001**
	IKDC 6 WEEKS	41.87	20	9.74					
Pair 2	IKDC PREINJECTION	34.69	20	10.11	−8.66	7.09	−5.47	19	<**0.001**
	IKDC 6 MONTHS	43.35	20	9.8					
Pair 3	IKDC 6 WEEKS	41.87	20	9.74	−1.49	3.76	−1.77	19	0.093
	IKDC 6 MONTHS	43.35	20	9.83					
Pair 4	VAS PREINJECTION	7.8	20	1.24	2.05	1.32	6.96	19	<**0.001**
	VAS 6 WEEKS	5.75	20	1.80					
Pair 5	VAS PREINJECTION	7.8	20	1.24	1.85	1.46	5.66	19	<**0.001**
	VAS 6 MONTHS	5.95	20	1.64					
Pair 6	VAS 6 WEEKS	5.75	20	1.80	−0.2	0.89	−1	19	0.33
	VAS 6 MONTHS	5.95	20	1.64					

Table 2
Intragroup Comparison paired T test: Low Molecular Weight HA + PRP.

LMW		Mean	N	Std. Deviation	Paired Differences		t	df	P VALUE
					Mean Difference	Std. Deviation			
Pair 1	IKDC PREINJECTION	34.14	17	12.36	−9.56	8.082	−4.88	16	<**0.001**
	IKDC 6 WEEKS	43.70	17	10.68					
Pair 2	IKDC PREINJECTION	34.14	17	12.36	−10.15	8.29	−5.05	16	<**0.001**
	IKDC 6 MONTHS	44.29	17	10.95					
Pair 3	IKDC 6 WEEKS	43.71	17	10.68	−0.59	3.02	−0.80	16	0.434
	IKDC 6 MONTHS	44.29	17	10.95					
Pair 4	VAS PREINJECTION	7.65	17	1.41	2.06	1.56	5.44	16	<**0.001**
	VAS 6 WEEKS	5.59	17	1.77					
Pair 5	VAS PREINJECTION	7.65	17	1.41	1.94	1.44	5.58	16	<**0.001**
	VAS 6 MONTHS	5.71	17	1.72					
Pair 6	VAS 6 WEEKS	5.59	17	1.77	−0.12	0.78	−0.62	16	0.543
	VAS 6 MONTHS	5.71	17	1.72					

- Chronic pain or swelling of the knee for a minimum of 4 months
- Imaging findings of degenerative changes of the joint (Kellgren Lawrence 0 to III at X-ray evaluation)

- Exclusion criteria
  - Kellgren-Lawrence score > grade 3
  - Rheumatoid arthritis
  - Haematological diseases,
  - Severe cardiovascular diseases
  - Infections
  - Diabetes Mellitus
  - Patients in therapy with anticoagulants or anti aggregant

Table 3
Intragroup Comparison paired T test: High Molecular Weight HA +.

HMW		Mean	N	Std. Deviation	Paired Differences		t	df	P VALUE
					Mean Difference	Std. Deviation			
Pair 1	IKDC PREINJECTION	38.65	14	19.16	−4.71	4.74	−3.718	13	**0.003**
	IKDC 6 WEEKS	43.36	14	16.10					
Pair 2	IKDC PREINJECTION	38.65	14	19.16	−8.64	14.65	−2.205	13	**0.046**
	IKDC 6 MONTHS	47.29	14	19.68					
Pair 3	IKDC 6 WEEKS	43.36	14	16.10	−3.93	14.12	−1.041	13	0.317
	IKDC 6 MONTHS	47.29	14	19.68					
Pair 4	VAS PREINJECTION	7.14	14	1.41	1.29	1.20	3.994	13	**0.002**
	VAS 6 WEEKS	5.86	14	1.29					
Pair 5	VAS PREINJECTION	7.14	14	1.41	1.57	1.91	3.078	13	**0.009**
	VAS 6 MONTHS	5.57	14	2.03					
Pair 6	VAS 6 WEEKS	5.86	14	1.29	0.29	2.27	0.471	13	0.645
	VAS 6 MONTHS	5.57	14	2.03					

2.1. Procedure

A 20 ml sample of venous blood was drawn from the patient's cubital vein under aseptic precautions and mixed with 5 ml of citrate phosphate dextrose solution. A 2 ml sample was collected here to assess the patient's baseline platelet counts. The mixture was then divided equally into 4 vacutainers. The sample were then placed in a centrifuge and spun at 3500 rpm for 7 minutes. Using a needle, the buffy coat supernatant layer was removed leaving behind the red and white cell components of the blood. The collected sample was divided equally into two more vacutainers and spun at 3000 rpm for another 5 minutes.

The sample was then collected using a 5 ml syringe and a 2.5 ml sample of PRP is then obtained. 2 ml of this sample was injected into the affected knee joint. 0.5 ml of the remaining collected sample of PRP was sent for platelet count assessment once again to determine whether an adequate concentration of platelet was achieved.

The patients were assessed with a VAS score, subjective and functional knee scoring systems before the injection, at 6 weeks and 6 months' post injection during review. Post injection the patient was only prescribed oral tramadol with paracetamol tablets for 5 days and told to ice the knee three times a day.

2.2. Statistical Analysis

Using paired T test for intra group comparison and One way Anova test with Posthoc test for inter group comparison. P value of 0.05 was taken as significant.

3. Results

3.1. Intragroup analysis

3.1.1. PRP

IKDC scores between pre injection and 6 weeks show a mean difference in score of 7.18 which is a statistically significant increase in score where $P < 0.001$

IKDC scores between pre injection and 6 months show a mean difference in score of 8.66 which is a statistically significant increase in score where $P < 0.001$

Visual analogue scores (VAS) between pre injection and 6 weeks post injection show a mean difference of 2.05 which is a statistically significant reduction in VAS score where $P < 0.001$

VAS scores between pre injection and 6 months shows a mean difference of 1.85 which is a statically significant reduction in VAS score where $P < 0.001$

3.1.2. LMW HA + PRP

IKDC scores between pre injection and 6 weeks show a mean difference in score of 9.56 which is a statistically significant increase in score where $P < 0.001$

IKDC scores between pre injection and 6 months show a mean difference in score of 10.15 which is a statistically significant increase in score where $P < 0.001$

VAS between pre injection and 6 weeks post injection show a mean difference of 2.06 which is a statistically significant reduction in VAS score where $P < 0.001$

VAS scores between pre injection and 6 months shows a mean difference of 1.94 which is a statically significant reduction in VAS score where $P < 0.001$

3.1.3. HMW HA + PRP

IKDC scores between pre injection and 6 weeks show a mean difference in score of 4.71 which is a statistically significant increase in score where $P = 0.003$

IKDC scores between pre injection and 6 months show a mean difference in score of 8.64 which is a statistically significant increase in score where $P = 0.046$

VAS between pre injection and 6 weeks post injection show a mean difference of 1.29 which is a statistically significant reduction in VAS score where $P = 0.002$

VAS scores between pre injection and 6 months shows a mean difference of 1.57which is a statically significant reduction in VAS score where $P = 0.009$

4. Intergroup analysis

4.1. VAS Score

At 6 weeks comparing the VAS scores between all three groups shows that LMW HA + PRP had the highest difference in scores and the HMW +PRP group had the least difference though this difference is **not** statistically significant.

At 6 months comparing the VAS scores between all three groups shows that LMW HA + PRP had the highest difference in scores and

Table 4
Intergroup Comparison: One way Anova test.

	GROUPS	N	Mean	Std. Deviation	Statistics/mean squares	df2(welch)/F(Anova)	P VALUE
IKDC PREINJECTION	LMW	17	34.141	12.3588	91.487	0.48	0.622
	HMW	14	38.65	19.1551			
	PRP	20	34.69	10.1086			
	Total	51	35.594	13.6662			
IKDC 6 WEEKS	LMW	17	43.70588	10.6757	17.692	0.121	0.886
	HMW	14	43.35714	16.098			
	PRP	20	41.865	9.742272			
	Total	51	42.88824	11.85844			
IKDC 6 MONTHS	LMW	17	44.29	10.953	0.238	26.845	0.698
	HMW	14	47.29	19.68			
	PRP	20	43.35	9.832			
	Total	51	44.75	13.359			

	GROUPS	N	Mean	Std. Deviation	Statistics/mean squares	df2(welch)/F(Anova)	P VALUE
IKDC DIFFERENCE 6 WEEKS PREINJECTION	LMW	17	9.564706	8.082152	90.811	2.413	0.1
	HMW	14	4.707143	4.736514			
	PRP	20	7.175	4.972966			
	Total	51	7.294118	6.30601			
IKDC DIFFERENCE BASELINE 6 MONTHS	LMW	17	10.15294	8.288404	12.802	0.127	0.881
	HMW	14	8.635714	14.65079			
	PRP	20	8.66	7.086265			
	Total	51	9.15098	9.868381			
IKDC DIFFERENCE 6 WEEKS 6 MONTHS	LMW	17	0.588235	3.021978	45.107	0.72	0.492
	HMW	14	3.928571	14.12093			
	PRP	20	1.485	3.756997			
	Total	51	1.856863	7.869848			

	GROUPS	N	Mean	Std. Deviation	Statistics/mean squares	df2(welch)/F(Anova)	P VALUE
VAS PREINJECTION	LMW	17	7.65	1.412	1.857	1.027	0.366
	HMW	14	7.14	1.406			
	PRP	20	7.8	1.24			
	Total	51	7.57	1.345			
VAS 6 WEEKS	LMW	17	5.59	1.77	0.287	0.103	0.902
	HMW	14	5.86	1.292			
	PRP	20	5.75	1.803			
	Total	51	5.73	1.638			
VAS 6 MONTHS	LMW	17	5.71	1.724	0.634	0.2	0.819
	HMW	14	5.57	2.027			
	PRP	20	5.95	1.638			
	Total	51	5.76	1.75			

	GROUPS	N	Mean	Std. Deviation	Statistics/mean squares	df2(welch)/F(Anova)	P VALUE
VAS DIFFERENCE 6 WEEKS PREINJECTION	LMW	17	2.06	1.56	2.998	1.586	0.215
	HMW	14	1.29	1.204			
	PRP	20	2.05	1.317			
	Total	51	1.84	1.391			
VAS DIFFERENCE BASELINE 6 MONTHS	LMW	17	1.94	1.435	0.56	0.222	0.802
	HMW	14	1.57	1.91			
	PRP	20	1.85	1.461			
	Total	51	1.8	1.562			
VAS DIFFERENCE 6 WEEKS 6 MONTHS	LMW	17	−0.12	0.781	1.05	0.549	0.581
	HMW	14	0.29	2.268			
	PRP	20	−0.2	0.894			
	Total	51	−0.04	1.371			

the HMW + PRP group has the least difference though this difference is **not** statistically significant(Graphs 1).

4.2. IKDC Score

At 6 weeks comparing the IKDC scores between all three groups shows that LMW HA + PRP had the highest difference in scores and the HMW +PRP group had the least difference though this difference is **not** statistically significant.

At 6 months comparing the IKDC scores between all three groups shows that LMW HA + PRP had the highest difference in scores and the HMW + PRP group has the least difference though this difference is **not** statistically significant(Graphs 2).

5. Discussion

PRP and HA intra-articular injections are treatments that have been employed for over a decade in treatment of early knee OA and a final consensus has not been reached as to whether there is any benefit. As stated before studies have been ambiguous and there is also an element of industry funded studies showing more benefit than those privately funded.[4] Other studies have also stated that PRP and viscosupplementation are also effect treatments individually.[5] Our study has shed light on PRP and HA combined injections as well as an individual PRP injections (Tables 1–5,).

In our study there were a total of 51 subjects of which 20 patients received intra-articular PRP, 17 received intra-articular

Table 5
Intergroup comparison: Posthoc Test.

Dependent Variable	(I) group	(J) group	Mean Difference (I-J)	Std. Error	P VALUE
IKDC PREINJECTION	LMW	HMW	−4.5088	4.9843	0.64
		PRP	−0.5488	4.5559	0.992
	HMW	PRP	3.96	4.8125	0.691
IKDC 6 WEEKS	LMW	HMW	0.34874	4.357013	0.996
		PRP	1.840882	3.982519	0.889
	HMW	PRP	1.492143	4.206849	0.933
IKDC 6 MONTHS	LMW	HMW	−2.992	4.884	0.814
		PRP	0.944	4.464	0.976
	HMW	PRP	3.936	4.716	0.684
IKDC DIFFERENCE 6 WEEKS PREINJECTION	LMW	HMW	4.857563	2.214168	0.082
		PRP	2.389706	2.023856	0.47
	HMW	PRP	-2.46786	2.137857	0.486
IKDC DIFFERENCE BASELINE 6 MONTHS	LMW	HMW	1.517227	3.625416	0.908
		PRP	1.492941	3.313804	0.894
	HMW	PRP	−0.02429	3.500466	1
IKDC DIFFERENCE 6 WEEKS 6 MONTHS	LMW	HMW	−3.34034	2.856296	0.477
		PRP	−0.89676	2.610792	0.937
	HMW	PRP	2.443571	2.757854	0.652
VAS PREINJECTION	LMW	HMW	0.504	0.485	0.556
		PRP	−0.153	0.444	0.937
	HMW	PRP	−0.657	0.469	0.348
VAS 6 WEEKS	LMW	HMW	−0.269	0.602	0.896
		PRP	−0.162	0.55	0.954
	HMW	PRP	0.107	0.581	0.981
VAS 6 MONTHS	LMW	HMW	0.134	0.642	0.976
		PRP	−0.244	0.587	0.909
	HMW	PRP	−0.379	0.62	0.815
VAS DIFFERENCE 6 WEEKS PREINJECTION	LMW	HMW	0.773	0.496	0.274
		PRP	0.009	0.454	1
	HMW	PRP	−0.764	0.479	0.258
VAS DIFFERENCE BASELINE 6 MONTHS	LMW	HMW	0.37	0.573	0.796
		PRP	0.091	0.524	0.983
	HMW	PRP	−0.279	0.553	0.87
VAS DIFFERENCE 6 WEEKS 6 MONTHS	LMW	HMW	−0.403	0.499	0.7
		PRP	0.082	0.456	0.982
	HMW	PRP	0.486	0.482	0.576

LMW HA + PRP and 14 received intra-articular HMW HA + PRP. Assessing the effectiveness of the injections individually, all three groups showed a significant decrease in VAS score and a significant increase in IKDC score. When compared to pre-injection and follow up scores P is <0.05 in all of the three groups. This means that all three intra articular injections have a statistically significant effect on treatment of early osteoarthritis of the knee. Patients have better subjective pain scores as indicated by the decreasing VAS score and a better functional outcome as indicated by the increase in the IKDC score.

An intergroup comparison was done to answer the question as to which injection is most effective for treatment of early knee OA. The results of the intergroup comparison show that LMW HA+ PRP had the greatest difference in VAS and IKDC score and HMW + PRP had the least difference in VAS and IKDC score. The difference in the comparison of the three groups was not statistically significant, indicating that in our study all three injection combinations were satisfactory modalities of treatment for early OA of the knee joint.

Our study indicates that there is a role for intra articular PRP injections as well as viscosupplementation in early OA of the knee joint. Of the three studied groups there is evidence to suggest that LMW HA +PRP was the most effective injection though the benefit is not statistically significant. A larger sample size may effect this result and prove a statistically significant difference.

Our results are in accordance with the study performed by Patel et al demonstrating PRP is more beneficial than placebo injections in early OA of the knee joint.[6] Another study done by Jang et al showed similar results where IKDC and VAS scores showed statistically significant improvement as in accordance with out study.[7]Our study has shown that there are statistically significant positive effects of administering the studied intra articular injections in early knee OA patients, as seen in all of the three study groups.

As postulated HMW HA is said to have a more mechanical effect when given as an intra-articular injection and inhibits angiogenesis into the joint.[8] LMW HA having a lower molecular weight may allow for some biological response and therefor a better healing response within the articular joint cartilage.

HMW HA is a costly injection when compared to LMW HA and PRP. When taking into account the outcome scores of each group and also cost as a factor, LMW HA + PRP is the more appropriate injection for the treatment of early knee OA as it has the most benefit to cost ratio. HMW HA + PRP is high in cost and least effective.

6. Conclusion

From our study it is evident that intra articular injections of PRP, PRP + LMW HA and PRP +HMW HA are all effective treatments in early osteoarthritis of the knee joint, showing significant decreases in VAS scores and significant increases in IKDC scores. This indicates that all three studied treatment groups are effective and acceptable modalities of treatment for early osteoarthritis of the knee.

When comparing each injection with each other, it was found that there was no statistically significant difference in VAS and IKDC scores in all three groups. That being said, PRP + LMW HA

group did show the greatest difference in function and subjective outcome although not significant.

There were no significant complications observed during the duration of our study.

Conflict of interest

None.

Acknowledgements

There has not been any external funding or contributions from other companies in our carried out research. All treatment costs were paid by the patients receiving the injections.

References

1. Felson D. Osteoarthritis: New Insights. *Ann Int Med*. 2002;136(1):88.
2. Marx R. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004;62(4):489–496.
3. Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. *Interdisciplinary Toxicol*. 2013;6(3):111–12510.2478/intox-2013-0019.
4. Printz Jonathon O. Conflict of interest in the assessment of hyaluronic acid injections for osteoarthritis of the knee: an updated systematic review. *J Arthroplasty*. 2013;28.8:30–33.
5. Spaková,. Tímea, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil*. 2012;91:411–417.
6. Patel S, Dhillon M, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(2):356–364.
7. Jang S, Kim J, Cha S. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur J Orthop Surg Traumatol*. 2012;23(5):573–580.
8. Sattar A, Kumar S, West D. Does Hyaluronan have a role in endothelial cell proliferation of the synovium? *Semin Arthritis Rheum*. 1992;22(1):37–43.