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THE EFFICACY OF PLATELET-RICH PLASMA VERSUS VISCOSUPPLEMENT IN THE TREATMENT OF KNEE OSTEOARTHRITIS

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Abstract

Background: Osteoarthritis is the most common form of arthritis and knee joint is the most common joint affected. There is no cure for osteoarthritis, but the condition doesn't necessarily get any worse over time and a number of treatments are available to help relieve the symptoms. Lubrication or viscosupplement injections provide the joint extra lubrication and shock absorption, as well as decrease friction within the joint which may slow the progression of osteoarthritis. Biological therapies such as platelet-rich plasma (PRP), have been proposed to improve clinical and structural outcomes by delivering a high concentration of growth factors that mediate healing and remodeling. Patients and methods: in this study; 30 patients were randomly allocated into three groups; the 1st group received PRP, the 2nd received viscosupplement and the 3rd group received local anaesthetic as a control group. Results are evaluated clinically using visual analogue of pain scale and modified hospital for special surgery score at 2, 4 and 6 months. Conclusion: Both PRP and viscosupplement injection are safe and effective treatment options for knee osteoarthritis, with PRP being more cost effective and more physiological.

INTRODUCTION

Osteoarthritis (OA) is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage surface accompanied by new growth of cartilage and bone at the joint margins (osteophytes), cyst formation and sclerosis in the subchondral bone, mild synovitis and capsular fibrosis. Osteoarthritis is considered a dynamic phenomenon as it shows features of both destruction and repair. [1]

Osteoarthritis (OA) is a common disease of aged population and one of the leading causes of disability. Incidence of knee OA is rising by increasing average age of general population. [2] Conservative treatment of OA includes non-steroidal anti inflammatory drugs (NSAIDs) first, Splints, modification of daily Activities, intraarticular Injection of Corticosteroid, hyaluronic acid and/or PRP (platelet rich plasma). Modalities of physiotherapy (light/laser, paraffin and iontophoresis with dexamethasone) should always be considered. If, despite conservative measures, pain or deformity interferes with daily activities then surgical options is considered. [3]

Unfortunately, articular cartilage lesions, with their inherent limited healing potential, are hard to treat and a Challenging problem to slow, halt, or reserve its progression. A variety of agents, such as nonsteroidal anti-inflammatory drugs, glucosamine, chondroitin-sulphate, hyaluronic acid, and glucocorticoids have been proposed as non invasive solutions for pain treatment, improvement in function and ultimately modification of severe chondral

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degeneration and osteoarthritis with varying success rates. It has been hypothesized that Hyaluronic acid(HA), a key component of synovial fluid, or platelet-rich plasma(PRP), which contains various growth factors involved in the inflammatory/healing process, may be good therapeutic agents for osteoarthritis. [4]

Platelet Rich Plasma (PRP) is an autologous concentration of blood-derived human platelets in a small volume of plasma. The platelet concentration of human platelets in plasma is 2 to 4 times greater than that which is found in blood at baseline. It is a simple; relatively low- cost and minimally-invasive method that provide a natural concentrate of autologous growth factors GFs from the blood. This method is now being increasingly applied and investigated in clinical practice for treatment of osteoarthritis nerve injury, tendinitis, , cardiac muscle injury, bone repair and regeneration.[5]

The biological rational of PRP is that platelets provide delivery of a highly concentrated cocktail of growth factors to accelerate healing. Transforming growth factor present in PRP has been associated with chondrogenesis in cartilage repair. It causes amplification of chondrocyte proliferation with convincing clinical effects on degenerative knee cartilage, it was recently demonstrated that PRP increased hyaluronic acid concentration, stabilizing angiogenesis in patients with osteoarthritic knees. [6]

The types of PRP vary according to the commercial preparation system used, the platelet concentration, or the anticoagulant or activator used. It is classified according to the presence or absence of leukocytes, the utilization of activator agents and the final concentration of platelets, which results in four product types. [7]

- Type 1 a high leukocyte concentration with no Activation.
- Type 2 a high leukocyte concentration with activation.
- Type 3 a low or no leukocyte concentration without activation.
- Type 4 a low or no leukocyte concentration with activation

All of the products can also be classified as either A, having a platelet concentration five or more times greater than baseline, or B, having a platelet concentration less than five times that of the baseline, we must note that the presence of leukocytes is responsible for the most intense and slowest liberation of growth factors, especially the TGFb1. [7]

Currently, a wide range of studies is taking place in different fields of medicine in order to test the potential benefits of PRP in enhancing cellular anabolism and tissue regeneration. [8]

Hyaluronic Acid [HA] Produced by synoviocytes, fibroblasts and chondrocytes, is the major chemical component of human joint synovial fluid. It is essential for the viscoelastic properties of the fluid because of high viscosity, and has a protective effect on articular cartilage and soft tissue surfaces of synovial joints. [9]

In OA, the concentration and the molecular weight of HA are reduced, resulting in synovial fluid of lower elasticity and viscosity. This diluitional effects reduces hyaluronan synthesis and free radical degradation that is the factors which contribute to the lower concentrations of HA. When the viscoelasticity of synovial fluid is reduced, the transmission of mechanical force to cartilage may increase its susceptibility to mechanical damage. [10]

PATIENT & METHODS

This study is single blind randomized prospective study carried out on 30 patients suffering from primary knee osteoarthritis during the period from April 2014 to April 2015 with follow up period ranged from 6 months to 12 months with average follow up period 9months.

The patients included in this study has age range from 18 to 50 years, with history of at least 6 months' pain and/or swelling of the knee, imaging findings of degenerative changes of the joint grade 1, grade 2 after Kellgren and Lawrence, unimproved with medical treatment and physiotherapy for at least 3 months.

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Patient excluded from this study: Patient with secondary osteoarthritis, rheumatoid patients, post traumatic osteoarthritis, Patient with other knee diseases. (Degenerative lateral and/or medial meniscus), Grade 3, grade 4 of knee osteoarthritis, history of steroid injection at least last 3 months, Blood disease as Thrombocytopenia, Patients on aspirin, ibuprofen or anticoagulant Therapy, active infection, Tumor and/or metastatic disease, pregnancy

All patients were subjected to history taking, clinical examination and radiological investigations with special emphasize on knee pain, swelling, limitation of movement**,** testing of lateral ligaments laxity with varus or valgus stress and testing of the anterior and posterior cruciate ligaments with the drawer test. Imaging plain x-ray on knee on standing position was performed for grading.

The treatment started by conservative treatment in the form of oral and topical NSAIDs, chondrotine sulphate, glucosamine, and physiotherapy for three months before shifting to injection treatment. Informed consent was assured to all patients prior to injection.

Patient are randomly classified into 3 groups

- Group (A) for injection with PRP group 10 patients
- Group (B) for injection with Hyaluronic group 10 patients
- Group (C) for injection with Xylocaine group 10 patients as a control group.

Injections treatment*:*

The injection treatment was used after taking appropriate consent and the approval of ethical committee for 30 cases after failure of the conservative methods. Injection treatment consists of:

Platelet-rich plasma preparation:

Under complete aseptic technique a 45-ml venous blood was collected in a tube containing 5 ml of sodium citrate from every patient treated. Then two centrifugations (the first at 1,800 rpm for 15 min to separate erythrocytes, and the second at 3,500 rpm for 10 min to concentrate platelet) produced a unit of 5ml of PRP. All the procedures were performed in the same office setting. Volume used for the first injection within 2 h. The total number of platelets per milliliter in the PRP represented a mean increase of 600% compared with whole blood values, and an average of 2.8 million platelets were given to affected knee at every injection. The whole procedure may be repeated after two weeks for another set of injection. Before the injection, 10% citrate was added to the PRP unit to activate platelets.

Hyaluronic group:

Under complete aseptic technique a syringe 2(ml) of Hyaluronic acid (suplasyn 2ml; bionichepham swizerland). injected into joint, and procedure repeated every 2 weeks regularly for 3 times

Xylocaine group:

Under complete aseptic technique a syringe 3(ml) of (Xylocaine). Is injected into joint, and procedure repeated every 2 weeks for 3 times.

In every injection case regardless material injected the skin was sterilized and the injection was performed through a classic lateral approach using a 20-g needle the patient were instructed to limit the use of the leg for at least 24 hours, use cold therapy/ice on the affected area for pain. During this period, the use of non-steroidal medication was forbidden. During the treatment period, rest or mild activities (such as an exercise bike, mild exercises in pool) were indicated, and subsequently the gradual resumption of normal sport or recreational activities was allowed as tolerated.

Patients were clinically evaluated using visual analog of pain score Modified Hospital for Special Surgery Knee (HSS) Scoring System score at 2, 4 and 6 months after the first injection

Statistical analysis:

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 22) as follows :-

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Description of quantitative variables as mean, SD and range
Description of qualitative variables as number and percentag
Chi-square test was used to compare qualitative variables between groups.
Unpaired t-test was used to compare quantitative variables, in parametric data (SD<50% mean)'
Mann Whitney test was used instead of unpaired t-test in non parametric data
(SD>50%mean)
Correlation co-efficient test was used to rank variables versus each other positively or inversely.

RESULTS

The demographic data of all the patients in the three different study groups are comparable as shown in table (1).

	PRP Group		**Hyaluronic Group**		**Xylocaine Group**		**One-way ANOVA**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**P-value**
Age (years)	47.00	1.56	46.10	2.13	46.90	2.33	0.588	0.563
Height (cm)	158.40	2.01	156.90	2.96	156.00	1.56	2.891	0.073
Weight (kg)	79.00	7.60	79.30	5.29	78.80	8.23	0.012	0.988
BMI	32.10	3.14	32.20	2.49	32.50	2.64	0.057	0.945

Table (1) showing there was no statistical significant difference between the groups as regards the age, height, weight and BMI. as p-value> 0.05.

There was improvement in pain score of PRP group as mean HSS score raised from 19.5 to 28.5 as demonstrated in table (2), also showing there was improvement in pain score of hyaluronic group as mean score raised from 22 to 28, and there was improvement in pain score of xylocaine group as mean score raised from 19.5 to 21. These results showing there was statistical significant improvement between the groups toward PRP group. This effect was persistent at 6 months follow up, figure (1).

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Table (2) pain score, stability score and strength score between three groups before injection

	PRP Group		Hyalorunic group		Xylocaine Group		One-way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P-value
Pre pain score	19.50	3.69	22.00	2.58	19.50	3.69	1.844	0.178
Pre stability	22.80	1.69	23.80	1.93	23.80	1.93	0.970	0.392
Pre strength	7.00	2.58	8.00	2.58	8.00	2.58	0.500	0.612

Table (2) showing there was no statistical significant difference between the groups before injection regarding pain score, stability score and strength score

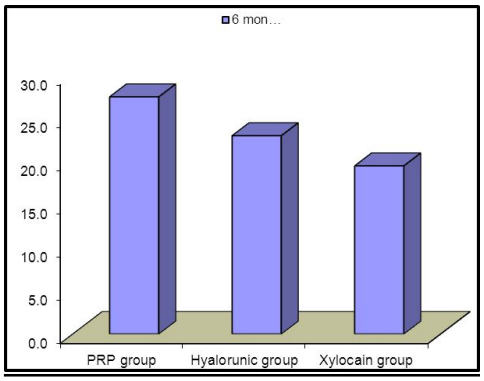

Figure (1): Pain incidence after 6 months.

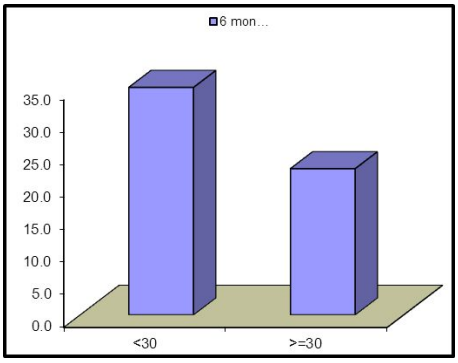

Figure (2): Pain incidence in relation to BMI in PRP group after 6months injection.

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Regarding the effect of weight on pain response after 6 months' injection in PRP group, figure (2) clarify that there is statistically significant difference between two subgroups 1st (BMI above 30) 2nd (BMI below 30), scoring system was higher in 1st group than 2nd group and it means patient with lower BMI respond more better than those patient with high BMI to PRP injection.

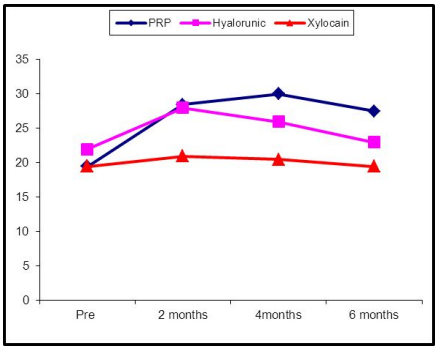

Figure* (3): *Pain course during period of the study

Figure (3) illustrate the response of three group to pain during period of study, in PRP pain score curve rise up especially during 1st 2 months and steady from 2nd to 4th months then lightly decline in last 2 months, in Hyalorunic pain score curve rise up especially during 1st 2 months and begin to decline from 2nd to 6th months, in xylocain group pain score curve appear as steady plateau, Thus, concluding that intra-articular therapy with PRP has time dependent effect with an average duration of 9 months improvement.

Regarding the response of three groups to strength during period of study, in PRP muscle strength score curve rise especially from 2nd to 4th then decline from 4th to 6th month, in Hyalorunic group strength score curve steady rise slightly from 2nd to 6th, in xylocain group strength score curve appear as steady plateau.

DISCUSSION

Viscosupplementation came into clinical use in Japan and Italy in 1987, in Canada in 1992, in Europe in 1995, and in the United States in 1997. Two hyaluronic acid products are currently available in the United States: naturally occurring hyaluronan (**Hyalgan fidia farmaceutici S.P.A Italy**) and synthetic hylan G-F 20 (**Synvisc sanofi Aventis U.S.A**). Hylans are cross-linked hyaluronic acids, which gives them a higher molecular weight and increased elasto-viscosity properties. The higher molecular weight of hylan may make it more efficacious than hyaluronic acid because of its enhanced elasto-viscosity properties and its longer persistence in the joint space. [11]

Platelet-rich plasma (PRP) is a natural source of concentrate of autologous growth factors from the blood. The procedure is simple, low cost, and minimally invasive; currently a wide range of researches is taking place in different fields of medicine in order to test the potential of enhancing tissue regeneration.

Most of the studies on autologous PRP injection have been focused on the reduction of pain and improvement of function over time. [11,12]

Wang-Saegusa et al (2011). Reported improvement of EQ-Visual analogue scale (EQ_VAS) and Western Ontario and McMaster Universities (WOMAC) scores at the 6-month follow-up in 261 patients with OA symptoms more than 3 months who had 3 intraarticular injections of autologous PRP at 2-week intervals. An improvement was documented in 192 of 261 patients with percentage 73.5% of patients and 71 of 261 patients with percentage 26.5 % had worse results.[12

Filardo et al (2011). reported that 3 injections of intra-articular PRP in (72 of 90) of the patients with percentage 80% with chronic knee degenerative conditions revealed improvement in International Knee Documentation Committee (IKDC) and EQ-VAS scores at the 2- year follow-up and that it had discernible positive

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effects especially on younger patients with early osteoarthritis in The IKDC objective score increased from 47% of normal and nearly normal knees before the treatment to 78% at the end, then to 73 and 67% at the 6- and 12- month follow-ups, respectively, showing a statistically significant improvement (P<0.0005) at all these follow-up times with respect to the basal level.[8]

Spakova et al (2012). reported a comparison study of PRP vs. hyaluronic acid in Kellgren-Lawrence grade 1, 2, or 3 osteoarthritis patients with better result in PRP group. The authors concluded that their preliminary findings supported the application of autologous PRP as an effective and safe method in the treatment of the initial stages of knee osteoarthritis and further studies were necessary to confirm these results and to investigate the persistence of the beneficial effects observed. [13]

In the present study the average age was 46.5 years old varying from 44 to 49years, this age was associated with higher incidence of knee osteoarthritis, (100 % of patients less than 50 years and 80%) had satisfactory results, and ***(Kon et al., 2011)*** reported that their patient's age ranged between 20-80 years old with mean age 47 years. Seventy patients of 81 with percentage 86.5% below 65years had satisfactory results and 3 of 10 with percentage 30% above 65 years had poor results, ***(Sampson et al., 2010)*** reported that their patients age ranged between 18 – 87 years, with a mean of 51.8 years, ***(Filorado et al., 2011)*** reported that their patients age ranged between 24-80 yrs, with a mean of 50 yrs. and has better results on younger patients according to IKDC patients below 35 years had 65% statically improvement while patients above 55 years had 50 % statically improvement.[2,6,8]

Also in our study we developed a reliable and low-cost manual protocol for preparing autologous PRP, in which we achieved average a platelet concentration 6 fold increased over baseline platelet count. Studies have shown that clinical efficacy can be expected with a minimum increase in platelet concentration of 4- to 6-fold from whole blood baseline (1million platelets/Kl). Some authors even recommend, without any scientific evidence, the elimination of leucocytes. However, several studies have already pointed out the key role of leucocytes in PRP for their anti infectious action, immune regulation, and promotion of angiogenesis**.** The leucocytes content did not seem to induce negative effects or to impair the potentially beneficial effects of PRP, even when used in joints. **,** however, we cannot conclusively claim that increased white blood cells in PRP have positive effect on knee joint, because we have no comparative data at this time.

In the present study a statistically significant improvement of clinical scores was obtained from the basal evaluation, the difference was found to be statistically insignificant (P value = 0.178) of Pre pain score between 3group then changed to (P value = 0.014) after 2month, changed to (P=0.028) after 4 months, changed to (0.010) after 6 months This evaluation was similar to p value on Spakova study (P value < 0.01) after 3months, (P value < 0.01) after 3months**.**

Guler et al. (2014) study had included 132 patients (mean age, 55.06 ± 8.41 years). Sixty-three patients were in the HA group and 69 patients were in the PRP group, [(14)] our study included 30 patients 10 patients were in the HA group 10 patients were in the PRP group, 10 patients were in the Xylocaine group. Increase in KSS score from post-treatment second month to post-treatment sixth month was significant (p\0.001). This increase was higher in the PRP group than in the HA group (difference between the scores in the HA group: 8.78 ± 3.28; difference between the scores in the PRP group: 10.85 ± 5.17; p = 0.008). [(14)] In the same study of ***Guler et al;*** while there was no difference between the groups in terms of pre-treatment KSS score, the PRP group had significantly higher KSS scores at the post-treatment second month and sixth month, also similar as in our study there was no difference between the groups in terms of pre-treatment (Modified Hospital for Special Surgery Knee Scoring System score MHSSNSS) the PRP group had significantly higher scores at the post-treatment second month fourth month and sixth month.[14]

In their prospective randomized study on 93 patients (119 knees)**; Alberto *et al. (2015)*** had minimum follow up of 2 years. Fifty knees were randomly selected prior to the first injection, to receive a second cycle at the completion of 1 year. A cycle consisted of three injections, each given at a monthly interval. The outcome was assessed using Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), Tegner and Marx scoring systems, recorded prior to the first injection and then at 12, 18 and 24 months. The study showed a significant improvement in all scores over time compared to the pre-treatment value ($p < 0.001$). At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Symptoms) and Tegner score,

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all other parameters showed a significant difference between the two groups in favor of the patients who had received the second cycle ($p < 0.001$). [15]

CONCLUSION

The preliminary short-term results of this study that show treatment with autologous PRP intraarticular injections is useful for the treatment of early degenerative articular pathology of the knee, aiming to reduce pain and improve knee function and quality of life however its efficacy is not much better than hyaluronic acid. PRP is cost effective modality but has time dependant response. However, more randomized controlled studies with longer follow up will be needed to confirm the real potential and to evaluate the durability and good regimen of this procedure. Further studies evaluating this new technique for treating cartilage degenerative pathology are in progress.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All authors declare that they have no conflict of interest related to this work.

Informed consent was obtained from all individual participants included in the study.

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