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Intraarticular Injection of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) in Early Knee Osteoarthritis

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Abstract

Introduction: This is a comparative study between HA and PRP injection in knee osteoarthritis. A total of 224 patients with knee osteoarthritis (grade I and II) were enrolled in this study. The arthritic changes were graded according to the Kellgren and Lawrence radiological scale. In the first group, 116 patients were intra-articularly injected with PRP three times with two weeks interval. In the second group, 108 patients were injected with three intra-articular injections of hyaluronic acid with two weeks interval. The patient's age and sex were comparable in both groups. In the PRP group, the mean of follow up was 30.34 months, while in the hyaluronic injection group, it was 28.886 months.

Results: At the end of follow, in the PRP group, 85 patients (73.3%) had satisfactory results, while 31 patients (26.7%) had unsatisfactory. The mean International Knee Documentation Committee score (IKDC) before injection was 53.747 ± 5.089 points, while at the end of follow up, it was 78.336 ± 7.676 points. In the hyaluronic group, 22 patients (20.4%) had fair results and 86 patients (79.6%) had poor results. The mean IKDC score before the injection was 53.787 ± 5.45 points, while at the end of follow up it was 56.36 ± 6.92 points. No complications were encountered during this study.

Conclusion: Intraarticular injections of PRP are safe, may be useful with long term effect in the treatment of early osteoarthritis knee. The patients' age and body weight has a significant effect on the final results.

Keywords: Platelet rich plasma; Knee osteoarthritis; Intra-articular injection; Hyaluronic acid

Introduction

Primary osteoarthritis (OA) of the knee can be defined as a process in which articular degeneration occurs in the absence of an obvious underlying abnormality [1]. The typical joints involved with primary osteoarthritis include the large, weight-bearing joints such as the hip and knee, as well as selected smaller joints in the hands, feet, and spine [2].

Primary OA knee is considered one of the most disabling orthopaedic problems in the middle age group. The problem is more evident in countries using kneeling in their religious traditions.

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 disability, and ultimately modification of severe chondoral degeneration and osteoarthritis with varying success rates [3].

Hyaluronic acid (HA) produced by synoviocytes, fibroblasts and chondrocytes, is the major chemical component of 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 joints [4].

In OA, the concentration and the molecular weight of HA are reduced, resulting in synovial fluid of lower elasticity and viscosity [5]. When the viscoelasticity of synovial fluid is reduced, the transmission of mechanical force to cartilage may increase its susceptibility to mechanical damage [6]. Treatment of knee OA with local injection of hyaluronic acid has been approved by the FDA, due to its superiority to placebo and other conservative treatments [7].

Platelet-rich plasma (PRP) is a natural concentrate of autologous growth factors from the blood [8]. The method is simple, low cost, and minimally invasive [8]. Autologous PRP is a volume of plasma having a platelet concentration above normative baseline values [9]. Platelets were thought to act solely in the clotting process. However, in addition to local hemostasis at sites of vascular injury, platelets contain an abundance of growth factors and cytokines that are crucial in soft tissue healing and bone mineralization [10].

PRP therapy provides delivery of a highly concentrated cocktail of growth factors to accelerate healing [11]. Platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, epithelial growth factor and insulin-like growth factor (IGF) were found in large amounts [11-13]. Transforming growth factor beta is active during inflammation, and influences the regulation of cellular migration and proliferation and stimulates cell replication [11,12]. Transforming growth factor β -2 present in PRP has been associated with chondrogenesis in cartilage repair [13].

The Authors performed this comparative study with the hypothesis that intraarticular administration of PRP could improve function and decrease pain in patients suffering from knee osteoarthritis.

Material and Methods

From August 2010 to August 2013, a comparative randomized clinical study was performed on two groups of patients. In the first group, three intra-articular knee injection of PRP; with two weeks interval; were given to 162 patients with osteoarthritis knee grade I and grade II according to the grading system of Kellgren and Lawrence [14]. During the study 46 patients were lost and did not show during follow up. At the end of follow up period 116 patients included in this study. The patient's age ranged from 45 to 60 years with a mean of 50.93 years. Seventy two patients were females while 44 patients were males. The right side was affected in 75 patients while the left side was affected in 41 patients. The follow up period ranged from 24 to 36 months from the first injection with a mean of 30.026 months (Table 1).

Table 1: Pre-injection clinical data.

Pre-Injection Data	PRP group	Hyaluronic Acid Group
1- Age	Range 45 y. to 60y. (Mean 50.93 y.).	Range 45 y. to 60y. (Mean 50.87 y.).
2- Sex	72 Females – 44 Males.	75 Females – 33 Males.
3- Side affected	Right side (75) – Left side (41).	Right side (68) – Left side (40).
4- Osteoarthritis grading	52 patients Grade I 64 patients Grade II.	50 patients Grade I 58 patients Grade II.

The second group includes 157 patients with knee osteoarthritis (grade I and grade II). In these patients three intra-articular injections of hyaluronic acid; with two weeks interval; were given in their knees. During the study 49 patients were lost and did not show during follow up. At the end of follow up period 108 patients included in this study. The patient's age ranged from 45 to 60 years old with a mean of 50.87 years. Seventy five were females and 33 were males. The right side was affected in 68 patients while the left side was affected in 40 patients. The follow up period ranged from 24 to 36 months from the first injection with a mean of 28.886 months (Table 1).

Selection to perform which procedure was done blindly without any patients or authors preference. Informed consent was taken from every participant in this study after full description of the whole procedures with their benefits and hazards. All patients signed this consent without any obligation. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

The inclusion criteria were patients with primary osteoarthritis knee grade I and grade II after failure of medical treatment for at least 3 months. The exclusion criteria are secondary osteoarthritis, grade III or more primary osteoarthritis, history of previous steroid injection, active infection elsewhere, patients with blood diseases like thrombocytopenia or patients receiving any anticoagulant medications.

Secondary OA was excluded after careful evaluation of all factors that could lead to OA by careful history taking, clinical examination, as well as laboratory and radiological investigation. Patients presented with knee effusion were also excluded temporary till the effusion resolved by rest, medications and remained as such for one month. The patients in the pre-injection condition were classified according to the grading system of Kellgen & Lawrence [14] into: Grade I and Grade II.

In the first group of patients (PRP group)

Under complete aseptic technique; about 30 ml. venous blood was collected in aseptic 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 3,200 rpm. for 10 min. to concentrate platelet) produced a unit of about 6 ml. of PRP.

One ml. of PRP was sent to the laboratory for analysis of platelet concentration, bacteriological test and quality test while the remaining (5 ml.) was used for intra-articular injection within 2 h. The total number of platelets in the injected PRP has an average of 5.3 millions (ranged from 4.7 to 6.2 millions).

Before the injection, one ml. of 10% Ca chloride was added to the 5 ml. PRP (one unit) to activate platelets. The whole procedure was repeated after two weeks for the second set of injection and after another two weeks for the third set of injection.

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The skin was sterilely dressed and the injection was performed through a classic lateral approach with the help of C arm Image in obese patients followed by flexion and extension of the knee few times, to allow the PRP to distribute itself throughout the joint. After the injection, the patients were sent home with instructions to limit the use of the leg for at least 24 hours and to use cold ice on the knee for pain. The use of non-steroidal medication was not allowed.

In the second group of patients

Three intra-articular injection of hyaluronic acid (concentration) with two weeks interval between each injection was performed in their knees. The injections were performed under complete aseptic technique with the help of C arm image intensifier in obese patients.

International Knee Documentation Committee score (IKDC) [15] was used to evaluate the patients clinically after 3 months, after one year and at the end of this study. Patients were asked to make post-injection X-ray after 6, 12, 18, 24 and 30 months. The changes present on X-rays were recorded and compared with previous x-rays. The data collected from this study were statistically analyzed using the mean (average), standard deviation, and T test.

Results

After 3 months from the first injection

In PRP group, and according to the IKDC scoring system; 24 patients (20.7%) had excellent results, 45 patients (38.8%) had good results, 34 patients (29.3%) had fair results and 13 patients (11.2%) had poor results in the PRP group. While in the hyaluronic group, 29 patients (26.9%) had excellent results, 39 patients (36.1%) had good results, 27 patients (25%) had fair results and 13 patients (12%) had poor results. The mean IKDC score for the first group was 72.81 ± 9.42 ranged from 45 to 86 points. While the mean IKDC score for the second group was 75.35 ± 9.06 ranged from 53 to 88 points. The difference was found to be statistically significant in favor of HA injection (P = 0.0407) (Table 2).

After one year from the first injection

And according to the IKDC scoring system; 28 patients (24.1%) had excellent results, 53 patients (45.7%) had good results, 24 patients (20.7%) had fair results and 11 patients (9.5%) had poor results in the PRP group. While in the hyaluronic group, 20 patients (18.5%) had good results, 51 patients (47.2%) had fair results, and 37 patients (34.3%) had poor results. The mean IKDC score for the first group was 75.38 ± 8.795 ranged from 51 to 86 points. While the mean IKDC score for the second group was 68.14 ± 7.75 ranged from 50 to 79 points. The difference was found to be statistically highly significant in favor of PRP injection (P < 0.0001) (Table 2).

At the end of follow up

And according to IKDC scoring system; 30 patients (25.9%) had excellent results, 55 patients (47.4%) had good results, 23 patients (19.8%) had fair results and 8 patients (6.9%) had poor results in the PRP group. While in the hyaluronic group, 22 patients (20.4%) had fair results and 86 patients (79.6%) had poor results. The difference was found to be statistically significant (P < 0.0001) (Table 2).

Table 2: The Functional results after 3 months, after one year and at the end of follow up period.

Follow p/Group	After 3 months				After one year				At the end of follow up			
	Sat.	Unsat.	Total	IKDC	Sat.	Unsat.	Total	IKDC	Sat.	Unsat.	Total	IKDC
PRP group	69	47	116	72.81±9.42	81	35	116	75.38± .79	85	31	116	78.34±7.67
HA group	68	40	108	75.35±9.06	20	88	108	68.14±7.75	0	108	108	56.36±6.92
Total	137	87	224	74.08±9.24	101	123	224	71.76± .27	85	138	224	67.35±7.29

Sat. means Satisfactory

Unsat. means Unsatisfactory.

After three months, the difference was found to be statistically significant in favor of HA group (P = 0.0407).

After one year, the difference was found to be statistically significant in favor of PRP group (P = 0.0001).

At the end of follow up period, the difference was found to be statistically significant in favor of PRP group (P = 0.0001).

In the PRP group and at the end of follow up period, the mean IKDC score before injection was 53.715 ± 5.0715 points ranged from 41 to 64 points. The mean IKDC score at the end of follow up period was 78.336 points ± 7.676 ranged from 52 to 88 points. A statistically significant improvement of all clinical scores was obtained from the basal evaluation (Table 2).

In the hyaluronic group the mean IKDC score before the injection was 53.787 ± 5.45 ranged from 44 to 64 points, while at the end of follow up period the mean IKDC score after the injection was 56.36 ± 6.92 ranged from 42 to 68 points. Most of the patients returned to the pre-injection level of activity or even got worse functional activity level.

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At the end of follow up period, 38 patients (73.07%) out of 52 patients with grade I knee osteoarthritis had satisfactory IKDC score after PRP injection with a mean of 79.269 points. While 47 patients (73.43%) out of 64 patients with grade II knee osteoarthritis had satisfactory IKDC score after PRP injection with a mean of 77.89 points. The difference was found to be statistically insignificant (P = 0.33).

Forty four patients (78.57%) out of 56 patients complaining of knee osteoarthritis less than 3 years had satisfactory IKDC functional results after PRP injection with a mean of 80.41 points. While 41 patients (68.33%) out of 60 patients complaining more than 3 years had satisfactory IKDC score after PRP injection with a mean of 76.35 points. The difference was found to be statistically significant (P = 0.004) (Table 3).

Table 3: The relation between the age, body weight, and duration of complaint with the functional outcome at the end of follow up period in the PRP group.

Age				Body Weight				Duration of Complaint			
Group	**Sat.**	**Unsat.**	**IKDC**	**Group**	**Sat.**	**Unsat.**	**IKDC**	**Group**	**Sat.**	**Unsat.**	**IKDC**
<50 years	46	4	81.8±5.51	<90 Kg.	48	5	81.92±5.49	<3 years	44	12	80.41±6.31
≥50 years	39	27	75.65±8.04	≥90 Kg.	37	26	75.27±7.99	≥3 years	41	19	76.35±8.33
Total	85	31	116	Total	85	31	116	Total	85	31	116

Sat. means Satisfactory

Unsat. means Unsatisfactory

As regard to the age, the difference was found to be statistically significant (P < 0.0001).

As regard to the body weight, the difference was found to be statistically significant (P < 0.0001).

As regard to the duration of complaint, the difference was found to be statistically significant (P = 0.004).

Forty six patients (92%) out of fifty patients below 50 years old had satisfactory IKDC functional results after PRP injection with a mean of 81.84. While 39 patients (59.09%) out of 66 patients above 50 years old had satisfactory IKDC score after PRP injection with a mean of 75.6515 points. The difference was found to be statistically significant (P < 0.0001) (Table 3).

Forty eight patients (90.56%) out of 53 patients less than 90 kg had satisfactory IKDC functional results after PRP injection with a mean of 81.924 points, while 37 patients (58.73%) out of 63 patients above 90 kg had satisfactory IKDC functional results after PRP injection with a mean of 75.269 points. The difference was found to be statistically significant (P < 0.0001) (Table 3).

There were no complications met with in this study. Most of the patients (88 patients) complained of mild to moderate knee pain for 2 to 3 days after the injection. Rest and ice application were successful in relieving most of that pain. No cases of intraarticular knee infection happened during this study.

Discussion

Most of the studies on autologous PRP injection have been focused on the reduction of pain and improvement of function over time [16,17]. Hyaluronic acid injection trials generally report positive effects on pain and function scores compared to placebo [6]. However, the evidence on clinical benefit is uncertain, due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported.

Platelet rich plasma may lead to proliferation of autologous chondrocytes and mesenchymal stem cells [13,17]. Increased hyaluronic acid secretion has also been noted in the presence of platelet rich rather than platelet poor preparation [18,19]. Osteoarthritic chondrocytes showed; after Platelet rich plasma injection; less interleukin-1 ß-induced inhibition of collagen 2 and aggrecan gene expression and diminished nuclear factor-B activation, which are the pathways involved in osteoarthritis pathogenesis [9,19].

Wang-Saegusa et al. [20] reported improvement of Western Ontario and McMaster Universities score (WOMAC) at the 6-month follow-up in 261 patients with OA symptoms who had three intraarticular injection of PRP. An improvement was documented in 192 of 261 patients (73.5%). Filardo et al. [21] reported improvement in International Knee Documentation Committee (IKDC) in 72 patients out of 90 patients two years after three intraarticular injection of PRP. Kon et al. [22] reported that intra-articular PRP injection in 100 patients with chronic degenerative condition of the knee had positive effects on improving pain and quality of life and on the scores of IKDC at the 1-year follow-up.

In this study, the maximal improvement in the hyaluronic injection group was after 3 months from the first injection. However the improvement was dramatically decreased after that until it became near the base line or even worse at the end of follow up period.

While in the PRP group; 85 patients (73.4%) had satisfactory IKDC score while 31 patients (26.6%) had unsatisfactory IKDC score after three knee intra-articular PRP injection. The mean IKDC score before injection was 53.747 points ± 5.089 points

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ranged from 41 to 64 points. The mean IKDC score at the end of follow up period was 78.46 points ± 5.925 ranged from 52 to 88 points.

In the PRP injection group, the number of unsatisfactory IKDC score was high (31 patients), but most of them were in the fair result group and have considerable improvement of their score with improvement of their activity level. Most of them felt that they perform better and more activity than before and some of them stop using NASIDs. Six patients continue using NASIDs at the end of follow up period.

Conclusion

At the end of follow up period and in the PRP injection group, patients with grade I osteoarthritis has better IKDC score than patients with grade II but with no statistically significant difference. In the PRP injection group, patients with less than 3 years complaint, patients less than 50 years old and patients weighing less than 90 kg had better IKDC score than patients more than 3 years complaint, patients more than 50 years old and patients weighing more than 90 kg and the difference was found to be statistically significant.

At the end of follow up period and in both study groups, there were no or little radiological changes between the first and last knee x rays. The radiological changes in grade I and grade II osteoarthritis before the injection were minimal and the expected radiological changes after the improvement were hard to detect. MRI study could be included in future authors' studies with special concern about the cost demand in our country.

Cerza et al. [23] found that, treatment with PRP showed a significantly better clinical outcome than did treatment with HA, with sustained lower WOMAC scores. Guler et al. [24] in a comparative study between PRP and Hyaluronic acid injection concluded that PRP appears to be an appropriate option for intraarticular treatment in patients with early-stage knee osteoarthritis.

The results obtained from his short-term are encouraging and indicate that treatment with autologous PRP intraarticular injections is safe, and may be useful for the treatment of early degenerative articular pathology of the knee, aiming to reduce pain and improve knee function and quality of life. Also a large number of patients (86.2% of patients) after improvement stopped using NASIDs with their side effects. Long term randomized controlled placebo studies are needed for firm and conclusive evaluation of this method of treatment in osteoarthritis.

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