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Comparative study of intra articular autologous platelet rich plasma and hyaluronic acid viscosupplementation in osteoarthritis of knee

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Abstract

Background: Osteoarthritis, the most common form of degenerative arthroses, affects the elderly resulting in physical, mental and social distress. In this study we are comparing the two different intra articular injections (Platelet Rich Plasma vs Hylan G-F 20) efficacy on osteoarthritis management.

Aims and Objectives: To compare the outcomes of intra articular injection of autologous platelet rich plasma versus hyaluronic acid viscosupplementation in osteoarthritis of knee.

Materials and Methods: In this study of 60 patients with OA knee who presented to CIO OPD, Safdarjung hospital after getting their informed consent, one group treated with PRP (group 1, n= 30) and the other with Hylan GF 20 (group 2, n = 30). In group 1, patients received 3 Intra articular injections of PRP at 4 weeks interval and in group 2, patients received a single Intra articular injection of Hylan GF 20 (Synvisc one). Institutional ethical committee approval obtained. SPSS version 17.0 was used for analysis.

Results: Baseline characteristics like age, sex, BMI of both groups were indifferent and comparable. Intra articular injections of PRP and Hylan GF 20 depicted improvement in both VAS and WOMAC index. PRP had a statistically significant better outcome than Hylan GF 20 from the fourth month of follow up in both sexes, in both age groups and in OA grade II and III. PRP was significantly better than hylan G-F 20 from the 6th month in BMI group of 18.5 to 24.99 and from the 5th month of follow up in patients with BMI more than 24.99.

Conclusion: Patients in both treatment group showed improvement whereas Intra articular PRP injection group had a statistically significant better outcome than Hylan G-F 20 from the fourth month of follow up.

Keywords: Hylan, intra articular injection, osteoarthritis, protein rich plasma

1. Introduction

Osteoarthritis (OA) of knee is an idiopathic, progressively debilitating chronic degenerative disease of joint. In this era of increasing active and aged population, osteoarthritis of knee calls out an alarm due to its adverse physical and social consequences [1-3]. Treatment options range from conservative method including physiotherapy and pharmacotherapy to surgical procedures including arthroscopic debridement and knee arthroplasty [4]. Intra articular viscosupplementation with hyaluronic acid (HA) is supposed to decrease pain and improve joint function [5, 6]. Intra articular PRP acts by limiting damage and promote healing mechanisms of cartilage involved. It acts by its anti-inflammatory, anabolic and local milieu altering mechanism through release of growth factor present in the platelets [7]. We in this prospective study included patients suffering from osteoarthritis of knee who satisfied inclusion and did not meet any exclusion criteria and randomized into two groups. One group received viscosupplementation of knee with Hylan G-F 20 and other with intra articular PRP and sequentially followed up for their efficacy.

Aims and objectives

To compare the outcomes of intra articular injection of autologous platelet rich plasma versus hyaluronic acid viscosupplementation in osteoarthritis of knee.

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Materials and methods

In concordance with the protocol submitted to the Guru Gobind Singh Indraprastha University, this study was carried out at the Central Institute of Orthopaedics, Safdarjung Hospital, and New Delhi from October 2012 to March 2014.

Study Design: This study was a prospective, randomized (closed envelope method), single blinded case series study with a total of 60 patients with 9 months follow up from the day of intervention.

Sample Size: Sixty patients with osteoarthritis knee who presented to CIO OPD, after randomization were consigned to two treatment groups: group 1 and group 2. Group 1 included thirty patients (n = 30) who received 3 doses of intra articular PRP at 4 weeks interval. Group 2 also included thirty patients (n = 30) who were given a single 6ml intra articular injection of Hylan GF 20.

Inclusion Criteria

- Consent for three intra articular injections
- Clinical and Radiological diagnosis of osteoarthritis
- Both sexes
- Body mass index between 18 and 35
- Clinical symptom more than 3 months
- Kellgren and Lawrence grade 1 to 3

Exclusion Criteria

- Hemoglobin < 10 g/dl
- Platelet count < 1,50,000/ cu.mm
- Kellgren and Lawrence grade 4
- Systemic disease including uncontrolled diabetes mellitus, immunosuppressive disorder, uncontrolled hypertension and cardiovascular disorders
- Coagulopathies and patient on anti-coagulant treatment
- NSAIDs use in the past 5 days
- Local dermatitis over the injection site
- Rheumatoid or polyarticular arthritis
- Allergy to egg products, bird feathers and avian products

Patients who presented to the CIO OPD with knee osteoarthritis who satisfied inclusion criteria and did not meet any of the exclusion criteria were subjected to the following evaluation

A detailed clinical history of the patient was elicited which included name, age, sex, address, occupation, telephone number, duration of symptoms, co morbid illness such as diabetes mellitus, hypertension, cardiac disorders, coagulation disorders or any immunosuppressive disorders

A general physical examination which included nourishment status, height, weight, body mass index, pallor, icterus, cyanosis and clubbing were done. Blood pressure and pulse of the patients were measured and recorded. Local examination of the affected knee/ knees of the patients were inspected for swelling, deformity, any local dermatitis, tenderness, synovial thickening, crepitus and range of motion

Routine blood investigations were done which include

- Complete blood count with platelets
- Random blood sugar
- Bleeding and clotting time

Plain antero posterior and lateral weight bearing radiograph of knee was taken. On the basis of the radiograph, osteoarthritic changes of knee were observed and patients were graded according to the Kellgren and Lawrence system from grade 1

to 3.

Patients were given patient information sheet and were explained in detail about the study. A full informed and written consent was obtained. After attaining the consent and randomization, baseline VAS and WOMAC index was assessed with the help of questionnaires. Patients were called for intra articular injection at their convenience. Patients who were to be given Hylan G-F 20 were asked to bring commercially available Hylan GF 20 (Synvisc one) on the day of intra articular injection

Intra articular injection-Hylan GF 20

Hylan GF 20 (Synvisc one) was prescribed which was a sterile insoluble gel containing of cross linked two hylan polymers namely hylan A and hylan B prepared from chicken coombs in a buffered physiological sodium chloride solution. Each Hylan GF 20 (Synvisc one) pack contained a prefilled 6 ml syringe and a 18 gauge needle. The syringe contains 6 ml of the following composition

- Hylan polymers (Hylan A + Hylan B) – 48 mg
- Sodium chloride – 51 mg
- Sodium dihydrogen phosphate monohydrate 0.24 mg
- Disodium hydrogen phosphate 0.96 mg
- Sterile water for injection

Platelet rich plasma

Under all aseptic precautions, about 8 to 10 ml of blood was extracted from the antecubital vein when PRP was to be injected into single knee. In case of injecting PRP into both knees, about 16-18 ml of blood was extracted. Extracted blood was collected in a sterile sodium citrate coated vial. With no delay, the blood was centrifuged at the rate of two thousand five hundred revolutions for two minutes in the centrifuge machine at department of blood bank, Safdarjung Hospital. PRP from the centrifuged blood was separated under all aseptic precautions. A small portion of it was used for measuring platelet count and the rest of PRP was immediately injected into the knee

Injection technique

- Patient laid in supine position
- Parts painted and draped
- A 18 – 22 gauge was inserted in the superolateral aspect of the knee joint into the suprapatellar pouch
- With a sterile syringe, joint effusion, if any was aspirated
- Three injections of 3 - 4 ml PRP were injected at 4 weeks interval in group I and a single injection of hylan GF 20 (Synvisc one) was injected in group II
- Sterile band aid was applied at the injection site
- Knee was flexed and extended few times after injection
- Patient were allowed to carry on their day to day routine activities.

Outcome analysis

The primary outcome measures are

- 100 mm Visual analogue pain scale
- Western Ontario and McMaster Universities Index of Osteoarthritis

Visual analogue scale is given to the patient before intervention which had a 100 mm scale with lower numbers denoting pain of less severity and higher numbers denote pain of more severity. This assessment was repeated at every follow up visit of the patient.

Western Ontario and McMaster Universities Index of

Osteoarthritis was used as a self-administered questionnaire in accordance with the developer's instructions. It included three sub divisions namely pain, stiffness and physical difficulty in doing daily activities. The possible scores range from 0 (best score) to 96 (worst score). The questionnaire contained 5 sub divisions under pain, 2 under stiffness and 17 under physical function. Each parameter could be scored from 0 to 4 based on the level of discomfort of the patient. This assessment was also done before intervention and during every follow up.

A strict vigilance was also done in view of any adverse reactions such as pain following injection, joint swelling or any systemic reactions.

Screening and baseline visit (day 0)

Before intervention, patient's records were noted in the proforma which included patients'

- Demographic data
- Brief history
- Examination findings
- Kellgren and Lawrence grade of osteoarthritis
- Laboratory findings
- WOMAC index/VAS scale at day 0 before intervention

Beyond the intervention, routine treatment was not changed and no additional diagnostic measures were demanded.

Follow up assessment

Hylan GF 20 was given as a single injection, whereas PRP was given as a three injection course at an interval of four weeks between two successive injections. Patients were followed up at 1 month, 2 month, 4 month, 5 month, 6 month and 9 month after first injection. In the PRP group, 2nd and 3rd injections were given at 1st and 2nd follow up visit.

During every follow up visit, the following were noted

- Date of visit
- VAS score and WOMAC score on the day of follow up visit
- Adverse reactions

None of the patients withdrew from the study before the amount of time had lapsed. The nine month follow up began for all patients from the date of first injection.

Statistical Method

Data were entered and analysed using statistical package for the social science

SPSS 17.0. Continuous variables are presented as mean \pm SD, and categorical variables are presented as frequency and percentage. Quantitative data was analysed using t test for comparing 2 groups. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

Results

This study was conducted at central institute of orthopaedics, Safdarjung hospital, New Delhi during the period of October 2012 to March 2014. Patients in both groups had either unilateral OA knee or bilateral OA knee. When bilateral knee was involved both the knees are taken into account. Group 1 had 30 patients with 38 knees involved and group 2 had 30 patients with 36 knees involved. In group 1, patients received three IA injections of autologous PRP at 4 weeks interval. The PRP injected was prepared from the Blood Bank, Safdarjung Hospital. In group 2, single IA injection of Hylan

GF 20 was given to patients. In patients with bilateral knee involvement IA injections were given in both knees simultaneously at each sitting.

The patients were followed up religiously. No patients withdrew from the study. All patients attended all follow up at 1st month, 2nd month, 4th month, 5th month, 6th month and at 9th month.

Mean age group of patients in group 1 (PRP) was 51.37 years (ranging from 37 years to 84 years) and in that of group 2 (Hylan G-F 20) was 50.7 years (ranging from 37 years to 71 years). In both groups majority of the patients were in the age group of 41 to 50 years two groups were statistically comparable both groups had 17 females and 13 males in each of them. Females were 56.7% of the total and the remaining 43.3% were males in group 1 of 30 patients (n=30), 38 knees were studied and in group 2 of 30 patients (n= 30), 36 knees were studied. In both the groups, right knee was predominantly involved.

Mean BMI of patients in group 1 was 27.07 (range from 21.9 to 34.3) and in group 2 was 25.49 (range from 20.7 to 31.2) 56.7% of patients in group 2 was in the BMI range of 18.5 to 24.9 whereas group 1 had 36.7% in this range OA grade II was more common among both the groups, followed by grade III and then by grade I. In group 1, OA grade II contribute 52.6% and in group 2, it was 58.3%

Discussion

Osteoarthritis, the most common form of degenerative arthroses, affects the elderly resulting in physical, mental and social distress. Osteoarthritis most commonly affects the knee and is more common in elderly women.

Many treatment options were used in the past with the goal of decreasing pain and improve the joint function. They included physiotherapy, life style modifications such as weight reduction and activity modifications, orthotics and pharmacological therapy such as oral NSAIDs, Opioids, glucosamine and chondroitin supplementation and intra articular injections of steroids and hyaluronic acid. Surgical options included arthroscopic lavage, debridement in cases of loose bodies and torn menisci and total knee replacement which is the last option in whom all medical management have failed and patients strive with intractable pain and disability.

Keeping this in mind, we decided to do this study to compare the efficacy of Hylan GF 20 viscosupplementation and autologous intra articular platelet rich plasma injection in OA knees.

Our study was a prospective randomized study with 60 patients and 9 months follow up. Patients were consigned to either of the two groups, after written and informed consent. In group 1 (n=30), patients received three IA injections of PRP (3 to 4ml) at 4 weeks interval. In group 2 (n=30), patients received single IA injection of Hylan GF 20. Follow up was done for 9 months from the date of first injection. In regards of usage of PRP, various authors used various plans of PRP injection. Cerza *et al.* used 4 injections at 1 week interval of volume 5.5 ml. Filardo *et al.* used 3 injections of volume 5 ml at 1 week intervals. Kon *et al* used 3 injections at 2 week intervals of volume 5 ml. Spakova *et al.* used 3 injections at 1 week intervals with volume of 3 ml [8-11].

No statistically significant differences were found regarding the baseline demographic patterns in the patients of both group. The mean age in group 1 was 51.37 years and in group 2 was 50.7 years. Each group contained 17 females and 13 males with 38 knees in group 1 and 36 knees in group 2.

Group 1 had 20 knees of OA grade II and group 2 had 21 knees of OA grade II. The mean BMI of group 1 was 27.07 and that of group 2 was 25.49.

The PRP prepared and used in this study had platelets amplified with an average of 4.07 times that of the baseline count. Aseptic precautions were carried out in each and every step of the PRP preparation process. Spakova *et al*, in their study, had an average 4.5 times amplification of platelet count [9].

The baseline VAS in group 1 and 2 were 62.21 and 62.5 respectively. In both groups there was reduction in the VAS score during follow up. The VAS score at the end of the study in group 1 and group 2 was 20.18 and 25.33 respectively. This fall in VAS is consistent in regard with both PRP and Hylan GF 20. In the study by Gobbi *et al*, patients treated with PRP had pre-treatment VAS of 4.1 ± 0.7 . VAS at 6 month follow up was 2.2 ± 0.4 and at 12 month follow up was 1.2 ± 0.3 . In the study by A. Kahan *et al*, patients treated with Hylan GF 20 had pre-treatment VAS of 61.1. VAS at 9 month follow up was 23.8 with a difference of -37.4 and p value of <0.0001 [12, 13].

The baseline WOMAC in group 1 and 2 were 61.24 and 58.28 respectively. In both groups there was reduction in the WOMAC score during follow up. The WOMAC score at the end of the study in group 1 and group 2 was 23.82 and 27.42 respectively. This is consistent with the study by Cerza *et al*, the pre-treatment WOMAC in PRP group who received 4

injections was 79.6 and at 4,12,24 month follow up was 49.6, 39.1 and 35.6 respectively [8]. Patel *et al* in his study among three groups, Group A (52 knees) received a single injection of PRP, group B (50 knees) received 2 injections of PRP 3 weeks apart, and group C (46 knees) received a single injection of normal saline, noted improvement in group who received 2 injections of PRP at 3 weeks interval (mean WOMAC score of 53.20; mean WOMAC scores at final follow-up of 6 months was 30.48). In group C, the mean WOMAC scores deteriorated from baseline (9.04, 2.70, 33.80, and 45.54, respectively) to final follow-up (10.87, 2.76, 39.46, and 53.09, respectively). The 3 groups were compared with each other, and no improvement was noted in group C as compared with groups A and B. There was no difference between groups A and B, and there was no influence of age, sex, weight, or body mass index on the outcome. [4] In the study by A. Kahan *et al*, patients treated with hylan G-F 20 had pre-treatment WOMAC of 46.3. WOMAC at 9 month follow up was 26.5 with a difference of -19.8 and p value of <0.0001 [13].

From the fourth month of follow up, there was significant difference between the two groups in improvement of VAS score and WOMAC score (VAS score -4th month p value - 0.003 and for the 5th, 6th and the 9th month, p value was less than 0.001. WOMAC-4th month p value - 0.046 and for the 5th - 0.032, 6th - 0.021 and the 9th month, p value was 0.01).

Table 1: Comparison of basic characteristics among two interventional groups

	PRP (n=30)		SYN VISC(n=30)		P Value
	Frequency	Percentage	Frequency	Percentage	
Age Groups[#](Mean \pm SD)	51.37 \pm 10.47		50.70 \pm 7.73		0.780 [#]
<=40 years	4	13.3%	2	6.7%	0.578*
41 - 50 years	13	43.3%	14	46.7%	
51 - 60 years	7	23.3%	11	36.7%	
61 - 70 years	5	16.7%	2	6.7%	
>70 years	1	3.3%	1	3.3%	
Sex*					
Female	17	56.7%	17	56.7%	1.000*
Male	13	43.3%	13	43.3%	
knee involved*					
Left	18	47.4%	17	47.2%	0.990*
Right	20	52.6%	19	52.8%	
BMI (Mean \pm SD)[#]	27.07 \pm 3.38		25.49 \pm 3.37		0.076 [#]
18.5 - 24.9	11	36.7%	17	56.7%	0.282*
25 - 29.9	12	40.0%	9	30.0%	
>=30	7	23.3%	4	13.3%	
OA grade*					
I	5	13.2%	5	13.9%	0.834*
II	20	52.6%	21	58.3%	
III	13	34.2%	10	27.8%	

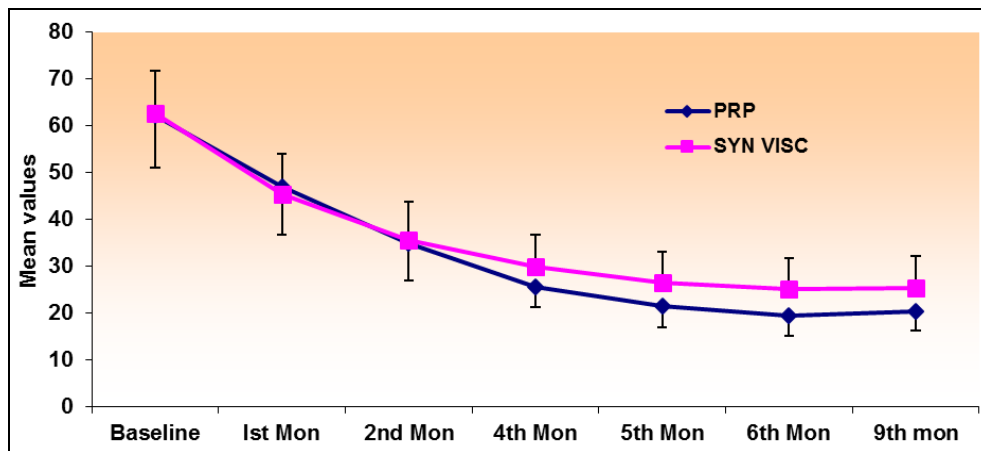
*Chi square test used, [#]T test used. P value <0.05 is significant

Table 2: Comparison of VAS score and WOMAC index between two groups

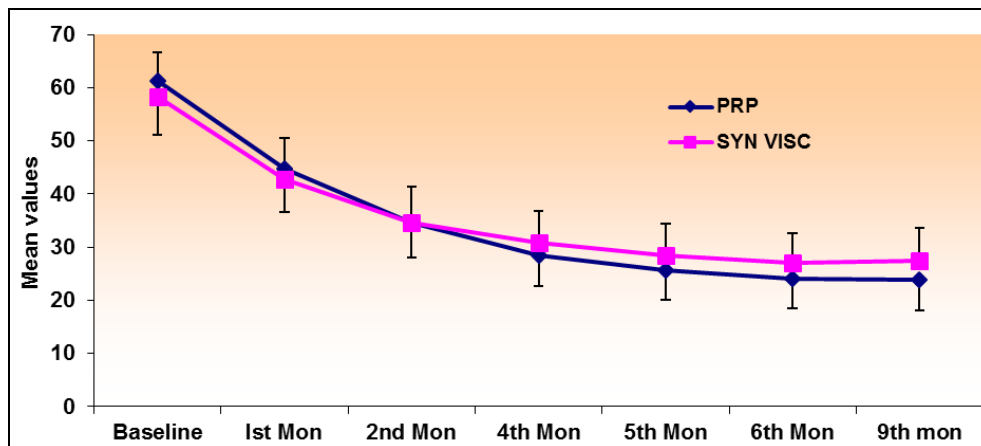
VAS	PRP (n=38)		SYN VISC (n=36)		P Value
	Mean \pm SD	Min - Max	Mean \pm SD	Min - Max	
VAS					
Baseline	62.21 \pm 11.30	40 - 80	62.50 \pm 9.25	45 - 80	0.905
1st Month	46.79 \pm 10.14	25 - 72	45.25 \pm 8.77	30 - 62	0.488
2nd Month	34.87 \pm 7.93	20 - 51	35.42 \pm 8.21	20 - 54	0.771
4th Month	25.58 \pm 4.49	15 - 34	29.72 \pm 6.87	15 - 42	0.003*
5th Month	21.39 \pm 4.52	10 - 30	26.39 \pm 6.60	12 - 36	<0.001*
6th Month	19.47 \pm 4.42	11 - 28	25.06 \pm 6.48	10 - 35	<0.001*
9th month	20.18 \pm 4.04	13 - 30	25.33 \pm 6.69	10 - 38	<0.001*
WOMAC index					
Baseline	61.24 \pm 10.18	42 - 78	58.28 \pm 8.28	42 - 76	0.176

Ist Mon	44.84 ± 8.19	31 - 58	42.67 ± 7.91	29 - 62	0.249
2nd Mon	34.53 ± 6.47	24 - 45	34.69 ± 6.68	21 - 51	0.913
4th Mon	28.39 ± 5.76	16 - 41	30.78 ± 6.01	20 - 42	0.046*
5th Mon	25.71 ± 5.57	14 - 39	28.36 ± 5.95	17 - 42	0.032*
6th Mon	23.97 ± 5.48	13 - 38	27.03 ± 5.63	18 - 37	0.021*
9th mon	23.82 ± 5.75	14 - 39	27.42 ± 6.11	16 - 39	0.011*

T test used. *P value <0.05 is significant



Comparison of VAS between PRP and SYN VISC group



Comparison of WOMAC between PRP and SYN VISC group

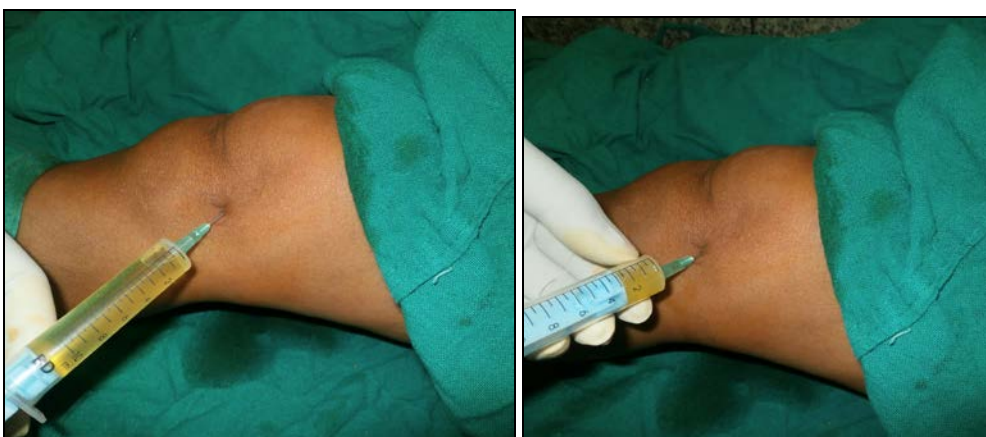
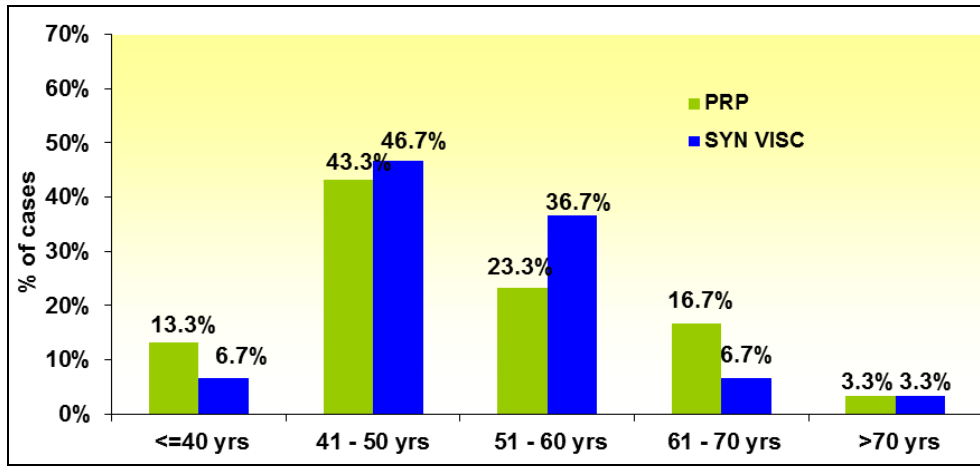
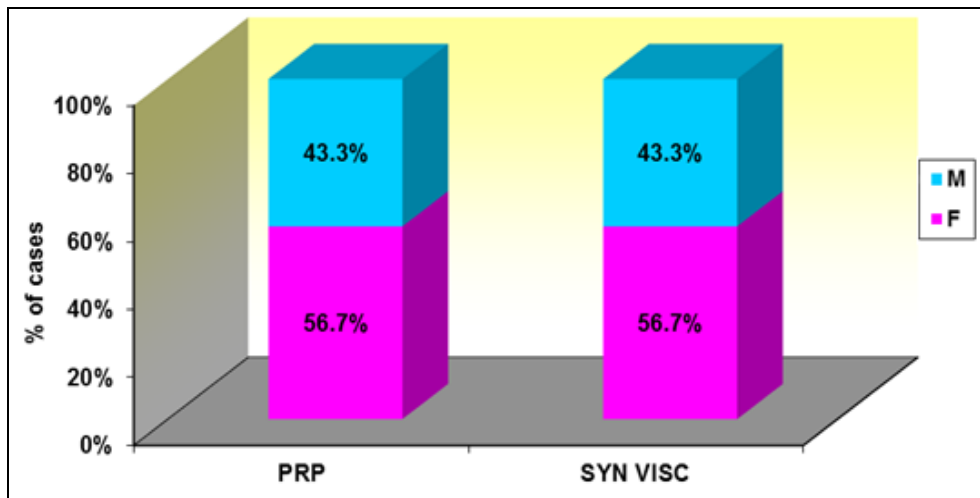


Image I: Procedure of Intra articular PRP injection to a patient.



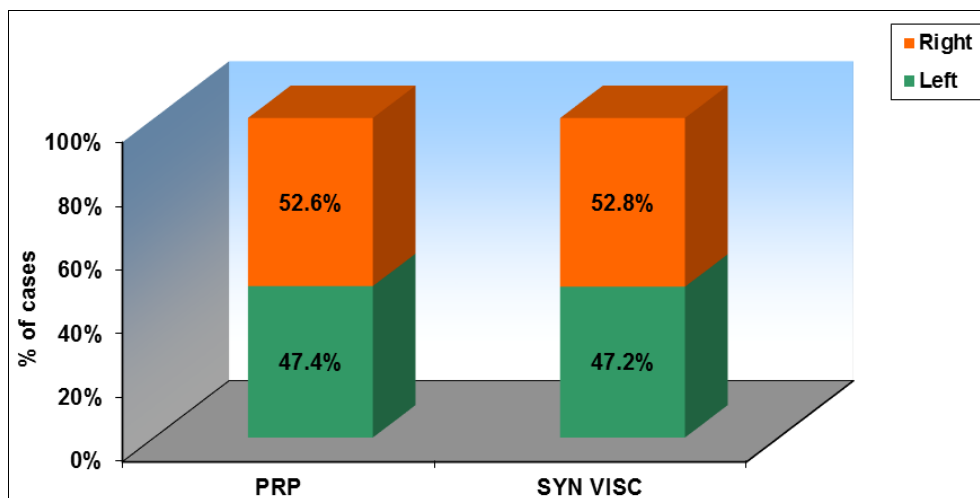
Comparison of Age distribution between PRP and SYN VISC group



Comparison of sex distribution between PRP and SYN VISC

Table 3: Side of the affected knee

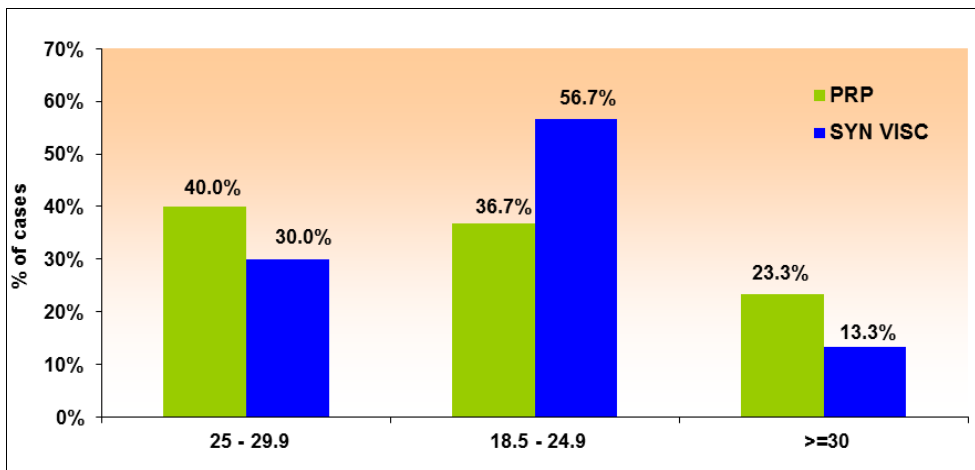
Knee involved	PRP		SYN VISC		P Value
	Frequency	Percentage	Frequency	Percentage	
Left	18	47.4%	17	47.2%	0.990
Right	20	52.6%	19	52.8%	
Total	38	100%	36	100%	



Comparison of knee involved between PRP and SYN VISC group

Table III: BMI of Patients

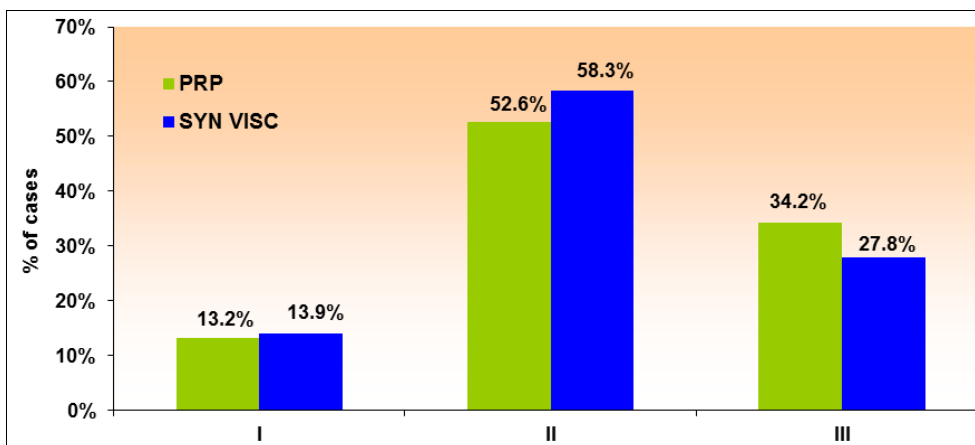
BMI groups	PRP		SYN VISC		P Value
	Frequency	Percentage	Frequency	Percentage	
18.5 - 24.9	11	36.7%	17	56.7%	0.282
25 - 29.9	12	40.0%	9	30.0%	
>=30	7	23.3%	4	13.3%	
Total	30	100%	30	100%	
Mean ± SD	27.07 ± 3.38		25.49 ± 3.37		0.076



Comparison of BMI distribution between PRP and SYN VISC group

Table IV: Radiological Grading Of Oa Knee

OA Grade	PRP		SYN VISC		P Value
	Frequency	Percentage	Frequency	Percentage	
I	5	13.2%	5	13.9%	0.834
II	20	52.6%	21	58.3%	
III	13	34.2%	10	27.8%	
Total	38	100%	36	100%	



Comparison of OA grade between PRP and SYN VISC group

Conclusion

In this study of 60 patients with OA knee, group 1 patients received 3 IA injections of PRP at 4 weeks interval and group 2 patients received a single IA injection of Hylan GF 20 (Synvisc one). The results of this study demonstrate that intra articular injection of either Hylan GF 20 or PRP is efficacious in the treatment of OA knee.

Intra articular injections of PRP and Hylan GF 20 depicted improvement in both VAS and WOMAC index in both sexes, in all age groups, in OA grades I, II and III, and in all BMI groups.

PRP had a statistically significant better outcome than Hylan GF 20 from the fourth month of follow up in both sexes, in both age groups and in OA grade II and III. PRP was

significantly better than hylan G-F 20 from the 6th month in BMI group of 18.5 to 24.99 and from the 5th month of follow up in patients with BMI more than 24.99

The limitations of this study were

- Sample size was less
- Follow up time was less. As there was decreasing trend in VAS and WOMAC in patients in the ninth month follow up, the long term effects warranted to be studied.
- Study was single blinded and not double blinded
- The role of concomitant life style modifications, physiotherapy and pharmacotherapy in addition to intra articular injections were ignored in this study.

These limitations when overruled in the future studies, a

better substantial treatment plan and the long term outcome of these two treatment modalities may get clarified.

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