Original Article

A Comparative Study on Effectiveness of Intra-articular Injection of High Molecular Weight Hyaluronate, Steroid and High Molecular Weight Hyaluronate plus Steroid in Osteo-arthritis Knee

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Abstract

Background: Although primary osteo-arthritis is well known as a benign degenerative condition, the impact of this disease course is becoming terribly disabling day to day in our community possibly because of increasing life expectancy. After lots of search regarding the role of intra-articular hyaluronic acid plus steroid in osteo-arthritis knee it is noted that scarcity of literature regarding conclusive evidence for the above. There is a grey zone regarding the combined role of these two agents in patients with primary osteo-arthritis. This project is a humble sincere attempt to find out the role of high molecular weight hyaluronate plus steroid in osteo-arthritis knee and to compare the effectiveness of this with intra-articular steroid, and intra-articular HMW hyaluronic acid.

Methods and Design: This is a single blind randomised controlled parallel group study conducted in the department of physical medicine and rehabilitation, IPGME & R, SSKM Hospital, Kolkata for a period of 18 months taking 27 subjects in each group. All patients with primary osteo-arthritis knee with grade two or grade three were included in the study group. And those who did not want to get incorporated in the study, patients with secondary osteo-arthritis knee, grade one or grade four osteo-arthritis knee, with gross knee instability, patients with contra-indications of intra-articular injections or intra-articular injection of steroid or with history of allergy to a viscosupplementation solution and patients received intra-articular injection in knee within last one year were excluded from the study. WOMAC pain, stiffness and functional subscales, VAS pain, ROM of knee joint, 50 feet walk time, Patients global assessment scale, Physicians global assessment scale were the parameters studied. After taking clearance from the institutional ethical committee, patients were selected based on the inclusion and exclusion criteria, and baseline (visit-1) assessment was done on the parameters. The selected patients have been divided into three groups randomly. Written informed consent was taken from all patients before interventions. One group received intra-articular injection of methylprednisolone, second group received intra-articular injection of high molecular weight hyaluronoic acid , and third group received intra-articular injection of high molecular weight hyaluronate plus methylprednisolone in the knee joint. The injections administered under strict aseptic condition. After administering injections, the patients assessed at the interval of 6 weeks (visit-2) and 12 weeks (visit-3) using the parameters mentioned above. The results have been analysed according to the standard statistical methods to fulfill the aims and objectives of the study.

Discussion: Majority of patients were female and more than 50 years of age with K-L radiological grade of 3. At the baseline visit, the WOMAC pain was comparable in all the three groups. It has been seen that, there was statistically significant improvement in all the parameters at the 2nd visit (6 weeks) from the baseline in all groups, and at the 3rd visit (12 weeks) though there was improvement on all the parameters from the 2nd visit in all groups, it was not statistically significant. Steroid, high molecular weight hyaluronate and steroid plus HMW hyaluronate all are effective in osteo-athritis knee in terms of reduction of pain, reduction of stiffness of knee joint, increase of range of motion of knee joint, reduction of 50 feet walking time, reduction of patients and physicians global assessment score. No treatment regime is statistically significantly better than the other group after 6 and 12 weeks of postinjection. Adverse effects of any treatment regime is negligible.

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Introduction:

Although primary osteo-arthritis is well known as a benign degenerative[1] condition, the impact of this disease course is becoming terribly disabling day to day in our community possibly because of increasing life expectancy. Even with the magical advent of the newer therapeutic treatment options, medical fraternity is still struggling to limit the disability of the so called benign disease. Until recent past intra-articular steroid was a good option to minimise patients' discomfort along with lots of experimental and inconclusive disease modifying drugs of osteo-arthritis. Recently intra-articular hyaluronic acid emerged as a newer weapon in the armamentarium of the physiatrists. After lots of search regarding the role of intra-articular hyaluronic acid plus steroid in osteo-arthritis knee it is noted that scarcity of literature regarding conclusive evidence for the above. There is a grey zone regarding the combined role of these two agents in patients with primary osteo-arthritis. This project is a humble sincere attempt to find out the role of high molecular weight hyaluronate plus steroid in osteo-arthritis knee and to compare the effectiveness of this with intra-articular steroid, and intra-articular HMW hyaluronic acid.

Aims and Objectives:

To compare the effectiveness of:

1) Intra-articular injection of high molecular weight hyaluronate,
2) intra-articular injection of steroid, and
3) intra-articular injection of high molecular injection of high molecular weight hyaluronate plus steroid in primary osteo-arthritis knee in relation to sign-symptoms as well as quality of life.

Materials and Methods:

Institutional ethical committee clearance has been taken for the study. Individual informed consent has been taken from patients to include in this study group. The study was conducted in the department of physical medicine and rehabilitation, IPGME & R, SSKM Hospital, Kolkata which extended from December 2010 to May 2012, and 27 subjects with primary osteo-arthritis knee who attended the OPD and osteo-arthritis clinic of the department of physical medicine and rehabilitation, SSKM Hospital, Kolkata, taken in each group. For the purpose of sample size calculation the pain component of the Western Ontario and McMaster University (WOMAC) index was considered as the primary outcome measure. It is estimated that 21 subjects would be required per group in order to detect a difference of 2 (two) in the WOMAC pain score with 80% power and 5% probability of type 1 error. This calculation assumes a standard deviation (SD) of 4 for this parameter and root mean square standardised effect of 0.5 assuming 20% drop out rate. This translates to a recruitment target of 27 subjects per group or 81 subjects overall. It was a single blind randomised controlled parallel group study. All patients with primary osteo-arthritis knee of grade two or grade three were included in this study, and grade one or grade four were excluded from the study. Those who did not want to get incorporated in the study, patients with secondary osteo-arthritis knee, or with gross knee instability, patients having contra-indications of intra-articular injection i.e. overlying soft tissue infection, bacteraemia, anatomic inaccessibility, an non-cooperative patient, etc, or patients with contra-indications of intra-articular injection of steroid i.e. infection in and around the joint, bacteraemia or sepsis, significant skin breakdown at the proposed injection site, presence of a joint prosthesis, uncontrolled diabetes etc, or with contra-indications of intra-articular high molecular weight hyaluronate i.e. allergy to a viscosupplementation solution excluded from the study. Patients who received intra-articular injection in knee within last one year also not included in the study.

Parameters studied:

1) The Western Ontario and McMaster Universities (WOMAC) index of osteo-arthritis pain subscale (out of 20), stiffness subscale (out of 8), and functional subscale (out of 68).The WOMAC 4-point Likert scale was used for this purpose.
2) Pain in visual analogue scale (VAS) score (out of 10).
3) Range of motion of knee joint (in degrees).
4) 50 feet walk time (in seconds).
5) Patients global assessment. For this, patients were asked to rate their overall condition considering pain, stiffness, swelling, activities of daily living and overall status, which was measured as out of ten (10) scale.
6) Physicians global assessment. For this, the physician rated the overall condition of the patient considering pain, patients' general condition, disease activity, physical examination, lab and clinical parameters which were measured as out of ten (10) scale.

Study technique: First of all ethical committee clearance was taken. In this study patients suffering from primary osteo-arthritis knee have been selected for intervention according to inclusion and exclusion criteria. The selected

patients have been counselled about the disease and therapeutic modalities. They were examined and assessed at baseline (visit-1) first. Study parameters measured at the visit-1.

WOMAC 5 point Likert scale was used for measurement of pain, stiffness and functional parameters. A 10 cm horizontal visual analogue scale was also used for pain measurement. Range of motion was measured using goniometer. Fifty feet walking time was measured using a stopwatch and asking the patient to walk for a distance of 50 feet in bare feet with maximum speed which is comfortable. Patients and physicians' global assessment scales were used to see the overall condition of the patient. The selected patients have been divided into three groups randomly. One group received intra-articular injection of methylprednisolone, second group received intra-articular injection of high molecular weight hyaluronoic acid, and third group received intra-articular injection of high molecular weight hyaluronate plus methylprednisolone in the knee joint. The injections administered under strict aseptic condition (Figs 1&2).

After administering injections, the patients assessed at the interval of 6 weeks (visit-2) and 12 weeks (visit-3) using the parameters mentioned above. The results have been analysed according to the standard statistical methods to fulfill the aims and objectives of the study.

Intervention: All patients were educated regarding joint protection and lifestyle modification and all patients were advised exercises for osteo-arthritis knee. All patients were instructed to perform range of motion of knee exercises and to perform 3 to 5 sets of 8 to 12 repetitions per set per knee of quadriceps setting exercises, as well as 3 to 5 sets of 8 to 12 repetitions per set of wall slides[2]. Only paracetamol 1 g was advised as analgesic on SOS basis with a maximum tablets of two a day. For intra-articular injection, first of all written informed consent was taken from each and every patient. Forty (40) mg of methylprednisolone was given in symptomatic knee under aseptic condition (for steroid group of patients). The HMW hyaluronate group was given 6ml of HMW hyaluronate as single dose in symptomatic knee under aseptic condition. For 3rd group (combined group), first 40mg of methylprednisolone was injected under aseptic condition followed by injection of 6ml of HMW hyaluronate under aseptic condition in the same sitting in symptomatic knee. Before injecting any drug, aspiration was attempted under aseptic condition and fluid was aspirated as much as possible. All injections were administered blindly (i.e., without using ultrasonography) by a single person following standard techniques as mentioned on text books of Physical Medicine and Rehabilitation by Joel. A. Delisa.

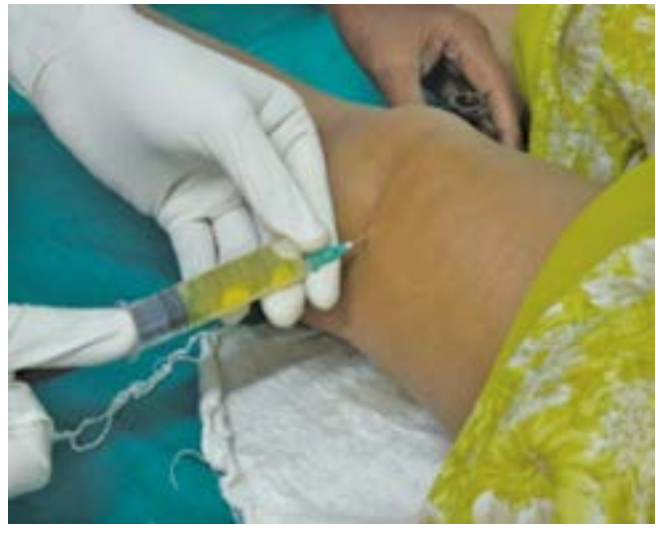

Fig 1- *Aspiration of Synovial Fluid from the Knee Joint*

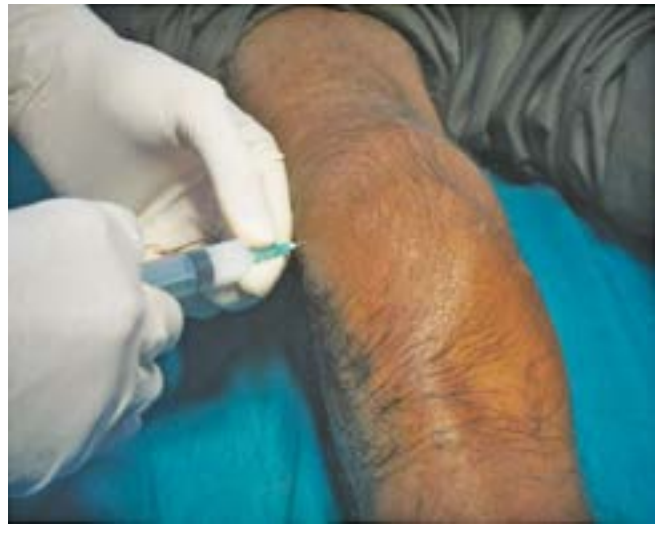

Fig 2- *Administration of Steroid into the Knee Joint*

Results:

Data have been summarised by usual description statistics such as mean and standard deviation (SD) for numerical variables that are normally distributed, and median and interquartile range for those that are not. Numerical variables have been compared between groups by one way ANOVA if normally distributed and Kruskall-Wallis ANOVA if otherwise. Appropriate posthoc test used to detect difference between to individual groups. Changes from baseline to study end have been assessed to repeated measure ANOVA for parametric variables and Friedman's ANOVA for non-parametric variables. Catagorical variables compared between groups by

Chi-square test or Fisher's exact test as appropriate. All analysis are two-tailed and $p < 0.05$ has been considered statistically significant.

Demographics:

In this study, out of total population of 66, 45 patients i.e., 79% were 50 years or more years of age with mean age of 59.35 years (Table 1 & Fig 3).

Table 1: *Descriptive Statistics for Age*

Age	No of cases	Mini-mum	Maxi-mum	Mean	Std deviation
Years	66	40	81	59.35	10.202

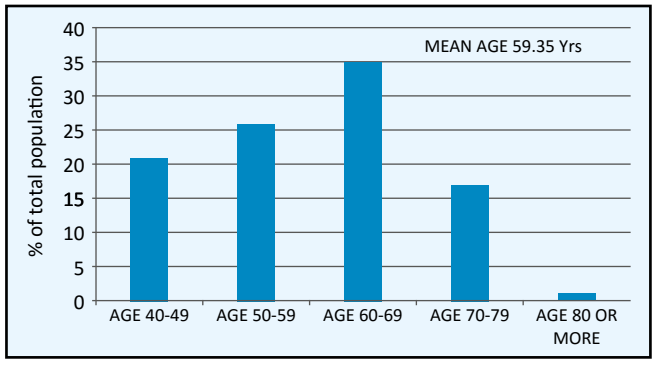

Fig 3- *Age Distribution*

Table 2 & Fig 4 show 60.6% of the total population were female and 39.4% were male, which is consistent with the fact that osteo-arthritis is more common in female population as revealed by other literatures also.

Table 2: *Descriptive Statistics (Frequencies) for Sex*

Sex	Frequency	Percent	Valid percent	Cumulative percent
Male	26	39.4	39.4	39.4
Female	40	60.6	60.6	100
Total	66	100	100	

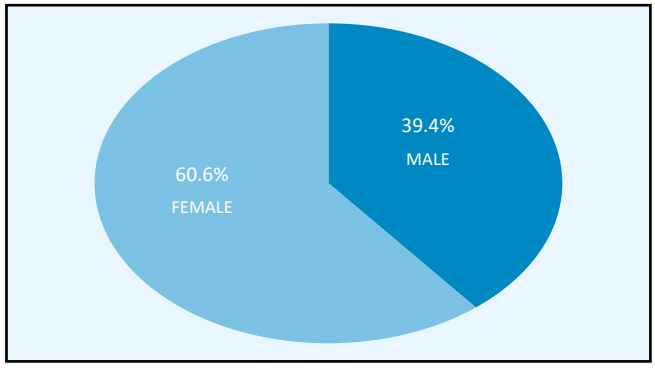

Fig 4- *Sex Distribution*

In this study 9.1% patients were overweight and 90.9% patients were within normal BMI range with mean BMI of 22.27 (Table 3 & Fig 5).

Table 3: *Descriptive Statistics for BMI*

	N	Minimum	Maximum	Mean	Std. deviation
BMI	66	20	27	22.27	1.525

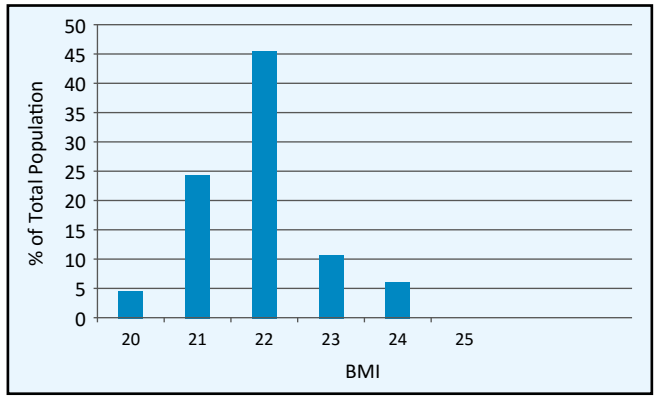

Fig 5- *BMI Distribution in Population*

In this study 11% patients had K-L radiological grade 2 osteoarthritis and 89% patients had K-L radiological grade 3 osteoarthritis (Table 4 & Fig 6).

Table 4: *K-L Radiological Grading*

K-L grade	Frequency	Percent	Valid percent	Cumulative percent
2	7	11	11	11
3	59	89	89	100
	66	100	100	

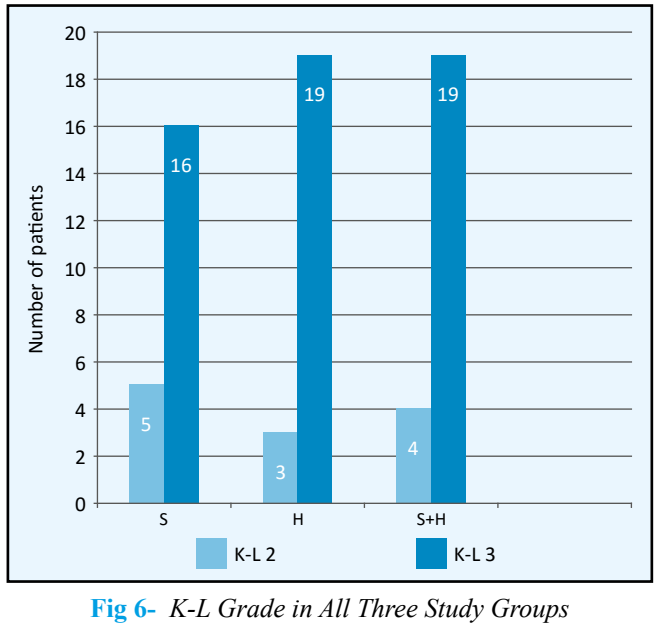

Fig 6- *K-L Grade in All Three Study Groups (K-L = Kellgren Lawrence grade)*

WOMAC Pain: (Tables 5 to 8)

WOMAC pain at visit 1 for all groups: P value: 0.4339; Number of groups: 3

Table 5: *WOMAC Pain at Visit 1, (S=Steroid Group, H=Hmw Hyaluronate Group, S+H=Steroid+Hmw Hyaluronate Group), NS=Not Significant*

Tukey's multiple comparison test	Mean difference	q	Significant <0.05	Summary	95% CI of difference
S VS H	-1.330	1.801	NO	NS	-3.838 to 1.178
S VS S+H	-0.4058	0.5430	NO	NS	-2.944 to 2.133
H VS S+H	0.9242	1.224	NO	NS	-1.642 to 3.490

So, at baseline visit, WOMAC pain was comparable in all the three study groups (p value= 0.4339).

Table 6: *Summary of WOMAC Pain, Stiffness and Functional Score in the Three Study Groups; (S=Steroid Group, H=HMW Hyaluronate Group, S+H=Steroid+HMW Hyaluronate Group)*

Pain	S	H	S+H	Between groups p value
Baseline	8.261	9.591	8.667	0.4339
6 Weeks	5.957	7.182	5.762	0.4760
12 Weeks	4.739	5.682	4.571	0.6707
Stiffness				
Baseline	1.478	1.773	1.810	0.8668
6 Weeks	0.8261	1.045	0.9524	0.8870
12 Weeks	0.5217	0.7727	0.7619	0.7748
Functional score				
Baseline	34.48	36.86	36.86	0.6280
6 Weeks	23.39	26.95	24.71	0.5690
12 Weeks	19.91	26.41	20.67	0.2076

Table 7: *Summary of VAS Pain Score, Range of Motion of Knee Joint and 50 Feet Walk Time in 3 Study Groups; (S=Steroid Group, H=HMW Hyaluronate Group, S+H=Steroid+HMW Hyaluronate Group)*

VAS pain	S	H	S+H	Between groups p value
Baseline	8.043	7.091	7.238	0.2116
6 Weeks	6.348	5.948	5.486	0.3226
12 Weeks	5.609	5.025	4.234	0.4234
ROM knee				
Baseline	122.2	127.9	125.0	0.6273
6 Weeks	125.2	129.5	126.4	0.7062
12 Weeks	128.3	131.4	127.9	0.7297
50 feet walk time				
Baseline	24.70	22.32	28.05	0.2646
6 Weeks	22.35	18.36	21.43	0.3628
12 Weeks	21.39	17.64	17.43	0.2895

Table 8: *Summary of Patients Global Assessment Score in 3 Study Groups; (S=Steroid Group, H=HMW Hyaluronate Group, S+H=Steroid+HMW Hyaluronate Group)*

	S	H	S+H	Between groups p value
Baseline	6.478	6.545	6.476	0.9760
6 Weeks	5.261	4.773	4.476	0.3613
12 Weeks	4.087	4.273	4.143	0.9475

Table 9: *Summary of Physicians Global Assessment Score in 3 Study Groups; (S=Steroid Group, H=HMW Hyaluronate Group, S+H=Steroid+HMW Hyaluronate Group)*

	S	H	S+H	Between groups p Value
Baseline	5.783	6.182	6.238	0.3477
6 Weeks	4.348	4.409	4.333	0.9908
12 Weeks	4.043	4.227	3.810	0.8099

Drop out (Fig 7): Table 9 shows physicians' global assessment. In this study in steroid group 4 patients out of 27 failed to follow-up. In HMW hyaluronate group, and in steroid plus HMW hyaluronate group 5 and 6 patients out of 27 patients in each group failed to follow-up respectively. So, the total drop out rate was 18.51%.

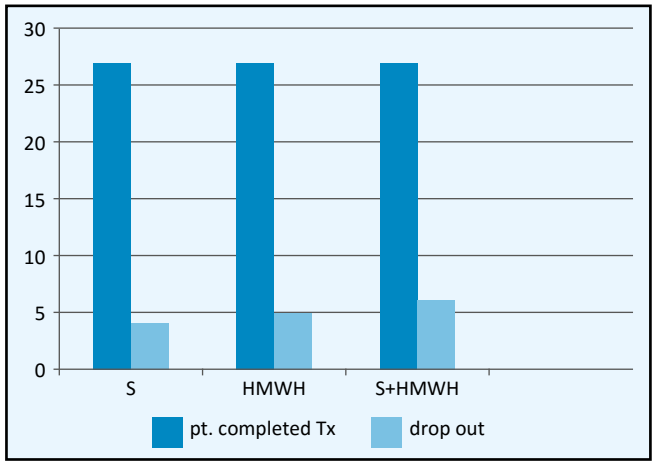

Fig 7- *Out in All Groups, S=Steroid Group, Hmw H= HMW Hyaluronate Group, S+HMW H=Steroid Plus Hmw Hyaluronate Group*

Adverse effects: Only two patients complained of local burning sensation during administration of 6ml of HMW Hyaluronate in knee joint. The burning sensation was transient and relieved after few minutes of administration of injection. No other adverse effects occurred in any group of patients.

Discussion:

The effectiveness of inta-articular injection of steroid[2] and high molecular weight (HMW) hyaluronate in osteo-arthritis knee has been claimed for a long[3]. There are some studies comaparing the effectiveness of the two in knee osteo-arthritis[4]. One study found, which showed the comparison of effectiveness between the two in shoulder osteo-arthritis. But, till date, no literature support could be achieved which showed comparison of effectiveness between intra-articular steroid, intra-articular HMW hyaluronate and intra-articular steroid plus HMW hyaluronate in osteo-arthritis knee.

This study showed that age is an important factor for the occurrence of osteo-arthritis as majority of the patients were old with mean age of 59.35 years. Majority of patients were female with 60.6% of total study population which suggests that osteo-arthritis is more prevalent in female population as supported by many literatures. Though obesity is an important factor for the occurrence of osteo-arthritis knee, the mean BMI (basal metabolic index) of this study population was 22.27. Majority of the patients had Kellgren-Lawrence grade 3 of osteo-arthritis with 89% of the total study population and rest of the population had grade 2 of osteo-arthritis. Grade 1 and grade 4 patients were not included in the study, as most of the grade 1 patients do not have significant pain and other discomforts, so detection of improvement could not be understood and comparison with other groups would not be appropriate. And in grade 4 patients it is very difficult to administer injection intra-articularly as the joint space is greatly impaired with presence of subchondral sclerosis in K-L grade 4 osteo-arthritis knee.

For WOMAC pain score, it has been seen that there was significant improvement of WOMAC pain score in all groups of patients. The improvement was significant at 6 weeks and at 12 weeks from the baseline visit in all groups, but the improvement at 12 weeks from 2nd visit (6 weeks) was not statistically significant in all groups. The difference of improvement of WOMAC pain in between groups was not statistically significant. The same pattern of improvement was there for all studied parameters i.e. WOMAC stiffness, WOMAC functional score, VAS pain score, 50 feet walk time, ROM of knee, patients global assessment score and physicians global assessment score within all groups with time and in between groups. So, the findings of the study suggest that no statistically significant difference was there between the three study groups. It is important to mention that very few patients in each group enjoyed pain reduction to zero on VAS scale, that is also for few weeks. In most of the cases pain intensity reduced, but never came to zero. So, none of the treatment option was able to reduce the pain completely. Onset of improvement of various parameters could not be determined, as while asking the

patients at 6 weeks about the onset of improvement of various parameters, most of the patients could not remember the exact time of onset. The duration of the improvement also could not be determined as the final follow up was at 12 weeks. So, better designed and better planned studies could be done to find out those in future. During routine OPD follow-up, two patients of HMW hyaluronate group reported about recurrence of symptoms after 8 months of postinjection. Total 15 patients failed to follow-up with total drop out rate of 18.51%. Only two patients complained of local burning sensation during administration of 6ml of HMW hyaluronate in knee joint and that was for few minutes. No other adverse reaction occurred in any group of patients, which suggests that all the treatment options are safe if not otherwise contra-indicated.

Limitations:

There were several limitations of the study. The limitations are :

1) No control group was taken.
2) Sample size was small in each group.
3) It was a short term study as the final follow-up was at 12 weeks, so it was not possible to know the treatment effects after 12 weeks postinjection.
4) Initial frequent follow-up and statistical analysis were not done.So this study has a limitation to conclude about the immediate postinjection effect.

Conclusions:

1) Osteo-arthritis is more prevalent in female population and in older age group.
2) Steroid, high molecular weight hyaluronate and steroid plus HMW hyaluronate all are effective in osteo-athritis knee in terms of reduction of pain, reduction of stiffness of knee joint, increase of range of motion of knee joint, reduction of 50 feet walking time, reduction of patients and physicians' global assessment score.
3) No treatment regime is statistically significantly better than the other group after 6 and 12 weeks of post-injection.
4) Adverse effects of any treatment regime is negligible.

Disclosure Statement:

This study was not funded by any governmental or non-governmental organisation or any pharmaceutical company, and no financial or other benefit was related to this study and no commitment or agreement was there to provide such benefit from a commercial entity.

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