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A Comparative Study to Assess the Efficacy Between Intraarticular Injection of Hyaluronic Acid Versus Intraarticular Injection of Hyaluronic Acid and Ketorolac in the Management of Osteoarthritis Knee

[1]Ankita Singha Roy, [2]Soumyadipta Ghosh, [3]Aniketa Banerjee, [4]Ishita Dey and [5]Pallab Das

[1,2,5]Department of Physical Medicine and Rehabilitation, R. G. Kar Medical College and Hospital, Khudiram Bose Sarani, Shyambazar, Kolkata, 700004, India

[3]Department of Physical Medicine and Rehabilitation, Midnapore Medical College and Hospital, Vidyasagar Road, Paschim Medinipur, Midnapore, 721101, India

[4]Department of Physical Medicine and Rehabilitation, Prafulla Chandra Sen Government Medical College and Hospital, Arambagh, Hooghly, 712601, India

ABSTRACT

An increasingly common degenerative condition that causes difficulty in elderly adults is osteoarthritis (OA).The knee joint is the most frequently affected joint. The symptoms of osteoarthritis (OA) in the knee include joint discomfort, pain, and reduced range of motion, crepitus, and sporadic effusion. To assess and compare the efficacy of intraarticular hyaluronic acid versus intraarticular hyaluronic acid and ketorolac in osteoarthritis knee. It was an Observational Prospective Analytical Study The study was conducted for 18 months This study was initiated after receiving the approval from the Institutional Ethical Committee of R. G. Kar Medical College and Hospital, 1, Khudiram Bose Sarani, Kolkata-700004,West Bengal. Of the patients in the Hylan Group, 9 (or 45%) had injections into the left side, whereas 11 (or 55%) received injections into the right side.Out of the total number of patients enrolled in the Hylan+Ketorolac group, 6 (30.0%) had injections on the left side and 14 (70.0%) on the right. There was no statistically significant association between the side injected and the groups (p = 0.3271). Among the patients in the Hylan Group the average body mass index (BMI) was 26.8600±3.3005.The participants in the Hylan+Ketorolac Group had an average body mass index (BMI) of 27.4800±2.6928, with a standard deviation of 2.6928. We could not find a statistically significant distribution of mean BMI with the groups (p = 0.5190). It is recommended to utilise injections of both hyaluronic acid and ketorolac. A large-scale clinical investigation comparing the efficacy of injecting hyaluronic acid and ketorolac into the knees of patients with osteoarthritis (OA) should be continued.

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Key Words
Osteoarthritis, intra-articular, hyaluronic acid, ketorolac and efficacy

Corresponding Author
Soumyadipta Ghosh,
Physical Medicine and Rehabilitation, R. G. Kar Medical College and Hospital, Khudiram Bose Sarani, Shyambazar, Kolkata, 700004, India
soumyapmr@gmail.com

Author Designation
[1]Junior Resident
[2,4]Assistant Professor
[3]Associate Professor
[5]Head

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INTRODUCTION

Disabilities caused by osteoarthritis (OA), a degenerative joint disease, are becoming more widespread among the elderly[1]. The knee is the joint that is affected most often. Pain, discomfort, restricted range of motion, crepitus and occasional effusion are clinical symptoms of knee OA. Walking impairment and cardiovascular disease are risk factors for OA mortality, according to some research[2]. Therefore, in treating OA, the goal is to reduce discomfort while simultaneously improving joint function. Palliative care, including multimodal, pharmacologic and surgical techniques, is the focus of treatment at the moment rather than cure. Pain management strategies often involve intra-articular injections of hyaluronic acid (HA), steroids, or non-steroidal anti-inflammatory medications (NSAIDS)[3-5].

By inhibiting chondrodegenerative enzymes and inflammatory processes, stimulating chondrocyte metabolism and synthesising articular cartilage matrix components, intra-articular hyaluronic acid may ameliorate symptoms of knee OA through several pathways[6].

The majority of NSAIDs given to patients with arthritis are oral NSAIDs. However, problems with the gastrointestinal system and kidneys can develop from using oral NSAIDS for an extended period of time[7]. Local tissue concentrations are increased and systemic problems are decreased when NSAIDS are given directly to the locations. While research on intra-articular NSAIDS is limited, what little there is suggests promising results. The research plan calls for a clinical diagnosis based on the patient's history and other diagnostic tools (such as radiography) to begin with. After that, we'll classify patients into two groups one will have just intra-articular hyaluronic acid, and the other will additionally get intra-articular ketorolac.

The study's outcome will be evaluated by comparing pre- and post-intervention scores on subjective and objective measures, such as the NRS and the WOMAC. The research variable's baseline parameters will be measured and recorded beginning one week before injection and again one week, four weeks and sixteen weeks after injection. The data that has been obtained will be organised and examined using the right statistical software.

MATERIALS AND METHODS

Method of data collection: The Institutional Ethical Committee of R.G. Kar Medical College and Hospital, 1 Khudiram Bose Sarani, Kolkata-700004, West Bengal, gave their clearance before the study could begin. A pre-tested and pre-designed study proforma was used to record the patient's history, important information from clinical examinations, and investigation reports. In a way that was easy for both the patients and their caregivers to comprehend, we went over each person's current health status as well as potential treatments, outcomes, and complications. Each participant gave their informed consent before being included in the study.

Type of study: Observational Prospective Analytical Study.

Study period: The study will be conducted for 18 months.

Study population: All the patients diagnosed clinically and radiologically will be counted in the study population, after considering inclusion and exclusion criteria.

Inclusion criteria:

- Age $\geq$50 years
- Unilateral or bilateral knee OA that meets the American College of Rheumatological criteria with Kellgren and Lawrence grade 2 and grade 3
- No improvement in pain after conservative treatment with oral NSAIDS or physiotherapy for atleast 6 months
- In patients with bilateral knee OA the most painful knee will be included in the study

Exclusion criteria:

- Age $\leq$50 years
- Grade 1 and Grade 4 knee OA according to Kellgren and Lawrence classification
- Past history of previous orthopaedic surgery of knee
- Any intraarticular therapy given to the patient 6 months prior to start of this study
- History of Rheumatoid arthritis
- History of gout
- History of any other inflammatory arthropathy
- Presently suffering from any severe neurological,psychiatric or any cardiac disorders that might interfere with the assessment during the study period
- Patient's refusal

RESULTS

Age in group: In Hylan Group, 12 (60.0%) patients were $\leq$70 years of age and 8 (40.0%) patients were 71-80 years of age. In Hylan+Ketorolac Group, 10 (50.0%) patients were $\leq$70 years of age and 10 (50.0%) patients were 71-80 years of age. Association of Age in Group with Group was not statistically significant ($p = 0.5250$).

Gender: In Hylan Group, 12 (60.0%) patients were Female years of age and 8 (40.0%) patients were Male. In Hylan+Ketorolac Group, 13 (65.0%) patients were

Table 1: Association between age in group Side injected with group

	Group			
Age in group	Hylan	Hylan+Ketorolac	Total	p-value
≤70	12	10	22	0.5250
Row %	54.5	45.5	100.0	
Col %	60.0	50.0	55.0	
71-80	8	10	18	
Row %	44.4	55.6	100.0	
Col %	40.0	50.0	45.0	
Total	20	20	40	
Row %	50.0	50.0	100.0	
Col %	100.0	100.0	100.0	
Side injected				
Left	9	6	15	0.3271
Row %	60.0	40.0	100.0	
Col %	45.0	30.0	37.5	
Right	11	14	25	
Row %	44.0	56.0	100.0	
Col %	55.0	70.0	62.5	
Total	20	20	40	
Row %	50.0	50.0	100.0	
Col %	100.0	100.0	100.0	

Table 2: Distribution of mean group with all parameter

Height (in cm)	No	Mean	SD	Minimum	Maximum	Median	p-value
Hylan	20	171.3	5.9569	155	180	172	0.3224
Hylan + Ketorolac	20	169.4	6.0298	158	178	169.5	
Weight							
Hylan	20	78.5	7.2946	65	90	79.5	0.8895
Hylan + Ketorolac	20	78.85	8.4808	65	92	79	
BMI							
Hylan	20	26.86	3.3005	20.5	32.9	26.4	0.519
Hylan + Ketorolac	20	27.48	2.6928	21.6	33.5	27.15	

Table 3: Distribution of mean WOMAC: Group

WOMAC (0)	No	Mean	SD	Minimum	Maximum	Median	p-value
Hylan	20	55.3000	8.0204	50.0000	77.0000	51.5000	0.2846
Hylan + Ketorolac	20	58.5500	10.7237	48.0000	79.0000	54.0000	
WOMAC (1)							
Hylan	20	46.9000	3.7262	44.0000	57.0000	45.5000	0.0294
Hylan + Ketorolac	20	51.7000	8.7244	42.0000	68.0000	48.5000	
WOMAC (2)							
Hylan	20	46.5000	7.4516	40.0000	63.0000	43.5000	0.0380
Hylan + Ketorolac	20	40.8000	9.2201	31.0000	60.0000	42.0000	
WOMAC (3)							
Hylan	20	41.2500	9.1759	30.0000	60.0000	40.0000	0.0176
Hylan + Ketorolac	20	32.9000	11.9292	18.0000	54.0000	30.5000	

Table 4: Distribution of mean NRS: Group

NRS (0)	No	Mean	SD	Minimum	Maximum	Median	p-value
Hylan	20	9	1.1698	7	7	9.5	0.4326
Hylan + Ketorolac	20	9.25	0.7864	8	8	9	
NRS (1)							
Hylan	20	7.9	1.2524	6	9	8.5	0.0039
Hylan + Ketorolac	20	6.7	1.2183	3	9	7	
NRS (2)							
Hylan	20	5.75	1.7733	3	8	6	0.0029
Hylan + Ketorolac	20	4.15	1.387	2	7	4	
NRS (3)							
Hylan	20	4.5	1.3955	2	7	4	<0.0001
Hylan + Ketorolac	20	2.05	0.394	1	3	2	

Female years of age and 7 (35.0%) patients were Male. Association of Gender with Group was not statistically significant (p = 0.7439).

Side injected: In Hylan Group, 9 (45.0%) patients had Left Side injected and 11 (55.0%) patients had Right Side injected. In Hylan+Ketorolac Group, 6 (30.0%) patients had Left Side injected years of age and 14 (70.0%) patients had Right Side injected Association of Side injected with Group was not statistically significant (p = 0.3271).

Height (in cm): In Hylan Group, the mean Height (in cm) (mean± s.d.) of patients was 171.3000±5.9569. In Hylan+Ketorolac Group the mean Height (in cm) (mean±s.d.) of patients was169.4000±6.0298. Distribution of mean Height (in cm) with Group was not statistically significant (p = 0.3224).

Weight: In Hylan Group, the mean Weight (in kg) (mean±s.d.) of patients was 78.5000±7.2946. In Hylan+Ketorolac Group the mean Weight (in kg) (mean±s.d.) of patients was 78.8500±78.8500.

Table 5: Group 0 (Hylan) Intra-group baseline to follow up changes

Multiple Comparisons

Dependent Variable	(I) gr	(J) gr	Mean Difference (I-J)	Std. Error	Sig.	95% confidence interval	Lower bound	Upper bound
WOMAC		0	4.85	2.508	0.22 -1.74	11.44		
		2	8.800*	2.508	0	2.21	15.39	
Turkey HSD		3	14.050*	2.508	0	7.46	20.64	
	1	-4.85	2.508	0.22 -11.44	1.74			
		2	3.95	2.508	0.4	-2.64	10.54	
		3	9.200*	2.508	0	2.61	15.79	
	2	0	2.508	0 -15.39	-2.21			
		1	-3.95	2.508	0.4	-10.54	2.64	
		3	5.25	2.508	0.17	-1.34	11.84	
	3	0	-14.050*	2.508	0	-20.64	-7.46	
		1	-9.200*	2.508	0	-15.79	-2.61	
		2	-5.25	2.508	0.17	-11.84	1.34	
NRS	0	1	1.400*	0.442	0.01	0.24	2.56	
Turkey HSD		2	3.550*	0.442	0	2.39	4.71	
		3	4.800*	0.442	0	3.64	5.96	
	1	0	-1.400*	0.442	0.01	-2.56	-0.24	
		2	2.150*	0.442	0	0.99	3.31	
		3	3.400*	0.442	0	2.24	4.56	
	2	0	-3.550*	0.442	0	-4.71	-2.39	
		1	-2.150*	0.442	0	-3.31	-0.99	
		3	1.250*	0.442	0.03	0.09	2.41	
	3	0	-4.800*	0.442	0	-5.96	-3.64	
		1	-3.400*	0.442	0	-4.56	-2.24	
		2	-1.250*	0.442	0.03	-2.41	-0.09	

The mean difference is significant at the 0.05 level.

Table 6: Group 1 (Hylan+Ketorolac) Intra-group baseline to follow up changes

Multiple comparisons

Dependent Variable	(I) gr	(J) gr	Mean Difference (I-J)	Std. error	Sig.	95% confidence interval	Lower bound	Upper bound
WOMAC		0	1	6.850	3.266	.163	-1.73	15.43
Turkey HSD		2	16.150*	3.266	.000	7.57	24.73	
		3	25.650*	3.266	.000	17.07	34.23	
	1	0	-6.850	3.266	.163	-15.43	1.73	
		2	9.300*	3.266	.028	.72	17.88	
		3	18.800*	3.266	.000	10.22	27.38	
	2	0	-16.150*	3.266	.000	-24.73	-7.57	
		1	-9.300*	3.266	.028	-17.88	-.72	
		3	9.500*	3.266	.024	.92	18.08	
	3	0	-25.650*	3.266	.000	-34.23	-17.07	
		1	-18.800*	3.266	.000	-27.38	-10.22	
		2	-9.500*	3.266	.024	-18.08	-.92	
NRS	0	1	1.900*	.337 .000	1.01	2.79		
Turkey HSD		2	4.450*	.337 .000	3.56	5.34		
		3	6.550*	.337 .000	5.66	7.44		
	1	0	-1.900*	.337 .000	-2.79	-1.01		
		2	2.550*	.337 .000	1.66	3.44		
		3	4.650*	.337 .000	3.76	5.54		
	2	0	-4.450*	.337 .000	-5.34	-3.56		
		1	-2.550*	.337 .000	-3.44	-1.66		
		3	2.100*	.337 .000	1.21	2.99		
	3	0	-6.550*	.337 .000	-7.44	-5.66		
		1	-4.650*	.337 .000	-5.54	-3.76		
		2	-2.100*	.337 .000	-2.99	-1.21		

The mean difference is significant at the 0.05 level.

Table 7: ANOVA

ANOVA

WOMAC	Sum of Squares	df	Mean square	F	Sig.
Between groups	7479.238	3	2493.079	23.369	p<0.0001
Within groups	8107.750	76	106.681		
Total	15586.988	79			
NRS					
Between groups	494.250	3	164.750	144.751	p<0.0001
Within groups	86.500	76	1.138		
Total	580.750	79			

Distribution of mean Weight (in kg) with Group was not statistically significant (p = 0.8895).

BMI: In Hylan Group, the mean BMI (mean±s.d.) of patients was 26.8600±3.3005. In Hylan+Ketorolac Group, the mean BMI (mean±s.d.) of patients was 27.4800±2.6928. Distribution of mean BMI with Group was not statistically significant (p = 0.5190).

WOMAC: Distribution of mean WOMAC (0) with Group was not statistically significant (p = 0.2846). Distribution of mean Woman (1) with Group was

statistically significant (p = 0.0294). Distribution of mean Woman (2) with Group was statistically significant (p = 0.0380). Distribution of mean Woman (3) with Group was statistically significant (p = 0.0176). NRS Distribution of mean NRS (0) with Group was not statistically significant (p = 0.4326). Distribution of mean NRS (1) with Group was statistically significant (p = 0.0039). Distribution of mean NRS (2) with Group was statistically significant (p=0.0029). Distribution of mean NRS (3) with Group was statistically significant (p<0.0001).

DISCUSSIONS

The demographical characteristics: An analytical prospective observational study was conducted. Careful consideration of inclusion and exclusion criteria led to the patient selection process. For knee osteoarthritis, one group (group 0) got intraarticular hyaluronic acid and another (group 1) got intraarticular hyaluronic acid with intraarticular ketorolac. The Out-Patient Department was used to identify patients based on their medical history and physical examination results.

At first, one hundred people were going to take part in this study. Because they did not fit the requirements for inclusion, 17 participants were left out. Forty-three people made up Group 1, while forty made up Group 0. Twenty people in group 0 and twenty-three in group 1 did not show up for their scheduled follow-up appointments and hence did not continue with the study. The study was only able to enrol 40 people. We did not include the drop-out participant's baseline or partial follow-up data in our statistical analysis.

Of the patients in Group 0, 12 were 70 years old or younger, and 8 were between the ages of 71 and 80, making up 60.0% of the total. In Group 1, 10 patients (or 50%) were 70 years old or younger, and 10 patients (or 50%) were between the ages of 71 and 80. When comparing the ages of Group 0 and Group 1, there was no discernible difference (p = 0.5250).

The gender breakdown plainly indicated that there were more women than men. A total of 40 people took part, with 25 women making up 62.5% and 15 men making up 37.5%. The gender breakdown was as follows 60% for Group 0 and 65% for Group 1. The gender association between Group 0 and Group 1 did not differ significantly from Group 1 (p = 0.7439).

Nine patients (45.0% of the total) in Group 0 had injections in their left knees and eleven (55.0%) in their right knees. Six patients (30.0%) in Group 1 had injections in the left knee and fourteen patients (70.0%) in the right knee. There was no statistically significant difference (p = 0.3271) between Group 0 and Group 1 in relation to the injection of sides. The patients were categorised according to the revised BG Prasad socioeconomic categorization scale, which was last updated in 2021, with regard to the per capita monthly income (in rupees).Out of the five groups, there were those classified as Upper Class (7770 and above), Upper Middle Class (3808-7769), Middle Class (2253-3808), Lower Middle Class (1166-2253) and Lower Class (<1166). The upper-middle class did not include any of these people. Although monthly per capita income does not influence osteoarthritis knee, patients from richer socioeconomic backgrounds are more likely to follow through with rehabilitation and make the necessary lifestyle changes.

The average age of the patients in Group 0 was 69.5500±5.5770.The average age of the patients in Group 1 was 70.2000±5.5022 years. We could not find a statistically significant distribution of mean age with group (p = 0.7127). The average height of the patients in Group 0 was 171.3000±5.9569 cm, with a standard deviation of 5.9569.Group 1 patients had an average height of 169.4000±6.0298 cm, with a standard deviation of 6.0298. No statistically significant relationship was found between the groups and the distribution of mean height (in cm) (p = 0.3224).
Patients in Group 0 had an average weight of 78.5000±7.2946 kg, with a standard deviation of 7.2946. The average weight of patients in Group 1 was 78.8500±78.8500 kg, with a standard deviation of 78.8500.Statistics showed no statistically significant distribution of group mean weight (in kg) (p = 0.8895). The average body mass index (BMI) of the patients in Group 0 was 26.8600±3.3005. The average body mass index (BMI) of the patients in Group 1 was 27.4800±2.6928.We could not find a statistically significant distribution of mean BMI with Group (p = 0.5190).

The average socioeconomic status (Mean±s.d.) of the patients in Group 0 was 3.1500±0.9881.At 2.9500±.9987, the mean socioeconomic status (SES) of patients in Group 1 was determined. A p-value of 0.528 indicates that there was no statistically significant distribution of mean SES with Group.

Discussion regarding outcomes of the study: The Western Ontario and McMaster University Osteoarthritis index score(WOMAC (0)) for patients in Group 0 was 55.3000±8.0204. Patients in Group 1 had an average WOMAC (0) of 58.5500±10.7237. We could not find a statistically significant distribution of mean WOMAC (0) with Group (p = 0.2846). Group 0 patients had an average WOMAC (1) score of 46.9000±3.7262, with 95% confidence intervals. The average WOMAC (1) score for patients in Group 1 was 51.7000±8.7244.There was a statistically significant distribution of the mean WOMAC (1) with respect to the Group (p = 0.0294, p<0.05).

Patients in Group 0 had an average WOMAC (2) score of 46.5000±7.4516. The patients in Group 1 had an average WOMAC (2) score of

40.8000±9.2201.There was a statistically significant distribution of the mean WOMAC (2) with respect to the Group ($p = 0.0380$, $p<0.05$). The average WOMAC (3) score for patients in Group 0 was 41.2500±9.1759.The average WOMAC (3) score for patients in Group 1 was 32.9000 with a standard deviation of 11.9292. There was a statistically significant distribution of the mean WOMAC (3) with respect to the Group ($p = 0.0176$, $p<0.05$). Therefore, we reject the null hypothesis (H0) and adopt the alternative hypothesis (Ha).

The average Numeric pain rating scale (NRS(0)) for patients in Group 0 was 9.0000±1.1698.The average NRS (0) calculated from the patients in Group 1 was 9.2500±0.7864.Statistical significance was not achieved ($p = 0.4326$) in the distribution of the mean NRS (0) with respect to Group. For patients in Group 0 the average NRS (1) (mean±s.d.) was 7.9000±1.2524.The average NRS (1) scores of patients in Group 1 were 6.7000±1.2183. It was statistically significant ($p = 0.0039$, $p<0.05$) to compare the distribution of the mean NRS (1) with the Group.

The average normal range score (NRS (2)) for patients in Group 0 was 5.7500±1.7733.Patients in Group 1 had an average NRS (2) of 4.1500±1.3870.It was statistically significant ($p = 0.0029$, $p<0.05$) to compare the distribution of the mean NRS (2) with the Group. The average NRS (3) (mean±s.d.) for patients in Group 0 was 4.5000±1.3955.Patients in Group 1 had an average NRS (3) of 2.0500±0.3940.It was statistically significant ($p<0.0001$) that the distribution of the mean NRS (3) with Group was different. Therefore, we reject the null hypothesis (H0) and adopt the alternative hypothesis (Ha). From baseline to week 16, there was a substantial difference in both group's WOMAC and NRS scores during the follow-up visits ($p<0.0001$).

CONCLUSION

Within the parameters of the trial, it was shown that injections of both hyaluronic acid and ketorolac were more effective than injections of hyaluronic acid alone in treating grade II and grade III osteoarthritis of the knee. Patients were encouraged to maintain their strength training routines, which included exercises to strengthen the quadriceps, hamstrings, and vastus medialis obliquus, during the course of the study. To maximise recovery in OA patients, further research is needed to determine the proper dosage and quantity of injections. It is recommended to utilise injections of both hyaluronic acid and ketorolac. A large-scale clinical investigation comparing the efficacy of injecting hyaluronic acid and ketorolac into the knees of patients with osteoarthritis (OA) should be continued.

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