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With Steroid, Without Steroid: Comparing Dual-Agent and Single-Agent Hyaluronic Acid Shots for Knee Osteoarthritis

Wheab Faraj Dawood^{*1}

1. Department of Orthopaedic Surgery, College of Medicine, Tikrit University, Iraq

* Correspondence: wheabsalih@gmail.com

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Abstract: Objective to compare the clinical efficacy and functional outcomes of a combined intra-articular injection of hyaluronic acid (HA) and corticosteroid against HA injection alone in patients with symptomatic knee osteoarthritis (OA). In this prospective comparative study, 62 patients with knee OA (Kellgren-Lawrence grade 2 and 3) were randomly allocated into two categories. The Combination Category (31 patients) received an injection contained both HA and corticosteroid in the first week followed by an injections of HA alone weekly for the next 2 weeks. The HA-only Category (31 patients) received an injection of HA alone weekly for three weeks. The primary outcome was the change in the Visual Analog Score (VAS) for pain at 1 month, 3-months and 6-months. Secondary outcomes included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and Patient Global Assessment (PGA). There was statistically insignificant differences regarding age, gender, BMI, stage of knee OA, baseline VAS, baseline WOMAC and baseline PGA between two categories. Both categories showed improvement from baseline in VAS and WOMAC scores at all follow-up intervals. the Combination Category demonstrated statistically superior results regarding VAS at 1-month, the mean reduction in VAS score was significantly greater in the Combination Category (31. 6±8. 3) compared to HA-only Category (42. 7±8. 9) with p value<0. 05. However, both categories demonstrated statistically insignificant differences at 3-month and 6-month follow up. The Combination Group showed superior result in WOMAC scores at 1-month follow-up, the mean reduction in WOMAC score was significantly more in Combination Category (32. 5±7. 2) in comparison with HA-only Category (41. 2±7. 6) with p value <0. 05. There was no statistically significant difference in WOMAC score at 3-month and 6-month between the two Categories. Patient Global Assessment (PGA) showed improvement from baseline at all follow-up time points. PGA showed statistically significant improvement at 1-month follow-up examination in Combination Category. Number of patients with good or very good assessment was 25 (80. 6%) in Combination Category while the number was 14 (45. 2%) in HA-only Category with p value <0. 05, but difference was insignificant at 3-month and 6-month follow-up. A combination therapy of corticosteroid and HA injection is significantly more effective than HA injection alone in providing rapid pain relief and early patient satisfaction within first month. However, for medium-term functional improvement at 3-6 months, both treatments are equally effective. The combination therapy is a valuable strategy for patients requiring rapid symptoms control while aiming for medium-term benefit.

Keywords: Knee Osteoarthritis, Hyaluronic Acid, Corticosteroid, Combination Versus Monotherapy.

1. Introduction

Osteoarthritis is a progressive long-term joint disease characterized by articular cartilage degeneration and bone overgrowth and affects 35% of adults in those older than 65 years [1]. Osteoarthritis of the knee either primary or secondary type according to cause. Articular cartilage degeneration in primary type is due to nonspecific cause while secondary OA is due to reason, which can be trauma, post-surgical trauma and malposition [2]. Knee discomfort, mobility problems and swelling knee are symptoms of knee OA. With ageing more individuals get chronic OA, this has a major impact upon people's health and life quality in those middle and elderly aged persons [3], [4], [5].

Knee joint injection can improve joint function and control pain for short term with decreased risk of patient injury [6], [7]. A glycosaminoglycan that is naturally found in synovial fluid in joints called HA act as a lubricant, with elastic properties and absorb shock during movement of the joint [8]. As OA of the knee become worse, the naturally occurring HA (endogenous) destroy from a high molecular weight (6500-10,900 kDa) to the lower molecular weight (2700-4500 kDa). Intra-articular HA injection improve viscosity of synovial fluid and lubricate joint, stop proteoglycan degradation with anti-inflammatory and analgesic advantages during OA treatment [9]. Hyaluronic acid has long duration of action [10].

Injectable corticosteroid block the production of inflammatory cytokines so exert anti-inflammatory effects [11]. Benefits from steroid injection has short term effect usually 1-4 weeks [12]. Corticosteroids are the gold standard in many international Societies guidelines [13], [14], [15]. For decades, corticosteroids have been used utilizing their anti-inflammatory action to provide symptomatic relief in treatment of knee OA [16], [17]. In this study, evaluation of the efficacy of using local steroid injection plus HA vs. HA injection alone in treatment of knee OA.

2. Materials and Methods

A sixty two patients participated in this prospective randomized, single blind parallel study. Selection was done randomly using a computer-generated list to those patients during the period between April 2022 and April 2024. 31 of them involved in category treated by local steroid injection plus hyaluronic acid and the other 31 patients treated by hyaluronic acid injection (HAI). Those patients attend an orthopedic out patients clinic for injection of the knee joint and for subsequent follow up checking at 1 month, 3 months and at 6 months after injection of the drugs. 50-65 years old patients were enrolled in this study and not all cases were included in it due to exclusion criteria in this study, cases excluded due to previous steroid injection or HA injection in the past 6 months, previous trauma causing intra-articular fracture of the knee, allergy to use of steroid drugs or HA, DM, knee surgery and history of previous infection or crystal induced arthritis, tumors of the knee joint, coagulations problems, infection or skin disease at the site of injection.

Patients were presented with at least three months with symptoms and signs of osteoarthritis confirmed by x-ray examination which revealed grade 2 or 3 knee OA according to Kellgren - Lawrence classification. Pain in those patients was not responded well or they not tolerated traditional treatment with non-steroid anti-inflammatory medications. Formal explanation for both treatments methods was done for both categories including follow up checking of the treatment.

VAS (visual analogue score) used to assess pain on a scale from 0-100mm, with 0 indicate no pain and 100 denote the most severe pain. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) was used to evaluate functional outcome also Patient Global Assessment (PGA). VAS, WOMAC and PGA were used at baseline, 1 month, 3 months and at six months.

Under aseptic non-touch technique, administration of drugs into the two categories of patients was done. Category 1 treated by a single injection of 80mg methylprednisolone plus 20 mg HA in the first week and HA injection alone in the two subsequent weeks and category 2 treated by injection of 20mg hyaluronic acid (HA) weekly for three consecutive weeks. In both categories injection was done through lateral retropatellar approach. Patients recommended to avoid activities such as tennis or jogging which are weight bearing activities also strenuous activities within forty-eight hours following the procedure.

Statistical analysis was done using SPSS 26 and p value of <0. 05 was significant.

3. Results

The mean age of the patients was 57. 43 years. The mean age for category 1 was 57. 8 years and the mean age for category 2 was 57. 1 years. 36 women and 26 men participated in this study. There was insignificant differences (p value> 0. 05) between two categories regarding patients age, gender, BMI, stage of knee OA according to Kellegran-lawrence (K-L) classification, baseline VAS, baseline WOMAC and baseline PGA (table. 1).

Table 1. Baseline characteristics.

Characteristic	Combination category (n=31)	Hyaluronic acid category (n=31)	P value
Age (years), mean $\pm$ SD	57. 81 $\pm$ 4. 74	57. 1 $\pm$ 4. 88	0. 546
Sex (female), n (%)	17 (54. 84%)	19 (61. 29%)	0. 607
BMI (kg/m ²), mean $\pm$ SD	28. 9 $\pm$ 2. 8	29. 4 $\pm$ 3. 1	0. 49
K-L Grade 3, n (%)	17 (54. 85%)	18 (58. 1%)	0. 80
Baseline VAS, mean $\pm$ SD	75 $\pm$ 9	73 $\pm$ 8. 1	0. 363
Baseline WOMAC, mean $\pm$ SD	59. 2 $\pm$ 6. 8	60. 5 $\pm$ 7. 1	0. 465
Baseline PGA (FAIR/POOR), N (%)	28 (90. 3%)	29 (93. 5%)	0. 641

Regarding VAS, it was improved in both combination treatment group and HA injection group from baseline scores even at 6months post injection. Combinations therapy category was improved more than HA injection treatment category and difference was statically significant (p value<0. 05), bur durig follow up checking at third month and sixth month, there was insignificant difference (p value >0. 05) between treatment methods (Table. 2).

Table 2. Outcome of treatment methods as measured by VAS (mean $\pm$ sd).

VAS (0-100)	Combination therapy	HA injection	P value
Baseline	75 $\pm$ 9	73 $\pm$ 8. 1	0. 363
1 month	31. 6 $\pm$ 8. 3	42. 7 $\pm$ 8. 9	0. 0001
3 months	36. 9 $\pm$ 9. 5	38. 5 $\pm$ 8. 7	0. 493
6 months	48. 4 $\pm$ 9	46. 5 $\pm$ 9. 8	0. 430

Functional improvement as measured by WOMAC (Table. 3), combination therapy category had a superior WOMAC score at 1 month (p value <0. 05)but both treatment methods achieved a good improvement at third month as compared with baseline scores although difference was insignificant between treatment methods (p value >0. 05). at 6 months, there was insignificant difference between two category (p value>0. 05).

Table 3. Treatment outcome as measured by WOMAC (mean $\pm$ sd).

WOMAC (0-96)	Combination therapy	HA injection	P value
Baseline	59. 2 $\pm$ 6. 8	60. 5 $\pm$ 7. 1	0. 465
1 month	32. 5 $\pm$ 7. 2	41. 2 $\pm$ 7. 6	0. 000
3 months	31. 7 $\pm$ 6. 8	34. 2 $\pm$ 7. 3	0. 168
6 months	39. 7 $\pm$ 7. 4	40. 1 $\pm$ 6. 8	0. 826

PGA revealed a higher proportion of satisfied patients at 1 month in category treated by combination therapy (p value<0. 05), also number of patients in combination therapy at three months was more but this was insignificant. By 6- month follow-up, PGA showed insignificant difference between two methods of treatment (Table. 4).

Table 4. Outcome of treatment methods as measured by PGA (number+%).

PGA (Good/Very good), n (%)	Combination therapy	HA injection	P value
Baseline	3 (9. 7%)	2 (6. 5%)	1. 000
1 month	25 (80. 6%)	14 (45. 2%)	0. 004
3 months	18 (58. 1%)	16 (51. 6%)	0. 610
6 months	10 (32. 3%)	11 (35. 5%)	0. 789

4. Discussion

The combination therapy in this study was beneficial. Adding corticosteroid to HA is important, and the primary advantage is the rapidity of early symptoms control. VAS pain reduced with a higher proportion of satisfied patients (PGA) in category treated by a combination therapy at 1-month interval. Early reduction of pain is clinically important, offering a bridge until the slower-acting HA take full effect. Patients treated by a combination therapy had superior WOMAC score at 1month, and both treatment methods achieved a comparable and significant improvement at 3-month. At 6-month follow-up checking, outcome measures (VAS, WOMAC, PGA) were statistically insignificant (p value>0. 05) between treatment groups. This denotes that the effect of steroid had waned, and long-term outcome was driven by HA in both categories.

Osteoarthritis Research Society International recommend injection of corticosteroid and HA for treatment of knee OA [18]. Analgesic effect of corticosteroid and hyaluronic acid have been proven by a number of studies [19], [20], [21], [22]. Treatment with HA injection might responded in a better way in patients without intra-articular inflammation. Euppaya et al., showed that therapy in form of HA injection plus anti-inflammatory drugs (corticosteroids or NSAIDs) was more effective for pain relief than HA injection alone in treatment of OA in 1-year period [23].

Cihat Ozturk et al., evaluate using HA injection alone with a combined treatment of HA and steroid injection in knee OA. this study showed that pain relief is considerable in patients treated by combination therapy of HA and corticosteroid injection with respect to VAS as well as WOMAC, and this combination demonstrated superior efficacy in achieving early pain reduction compared to treatment with HA lonely [24]. In study done by Jones et al. [25] found that while both HA and triamcinolone hexacetonide showed beneficial effects on pain of inflammatory knee OA for the first 5 weeks, HA demonstrated superior efficacy from 5 weeks to 6 months compared to triamcinolone hexacetonide (steroid drug). Bannuru et al. in a systematic review and meta-analysis about treatment of knee OA with HA vs corticosteroid conclude that corticosteroid injection is more effective than injection of HA from baseline to fourth week but equal in their efficacy by fourth week. HA shows greater efficacy after 8 weeks [26]. The results of these studies are comparable to the results in this study.

Regarding complications, two methods were safe, and the intra-articular injection was performed without complications.

5. Conclusion

A combination therapy of corticosteroid and HA injection is significantly more effective than HA injection alone in providing rapid pain relief and early patient satisfaction within first month. However, for medium-term functional improvement at 3-6 months, both treatments are equally effective. The combination therapy is a valuable strategy for patients requiring rapid symptoms control while aiming for medium-term benefit.

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