

Original Research Article

Clinical outcome of intra-articular hyaluronic acid injection for knee joint osteoarthritis: a prospective interventional study from a tertiary care hospital

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ABSTRACT

Background: The prevalence of knee osteoarthritis (OA) is estimated to be 14% and 6% in rural and urban areas of India, respectively. In severe cases, the American Academy of Orthopedics Surgeons recommends non-steroidal anti-inflammatory drugs (NSAIDs). A prospective interventional study was conducted to evaluate the effectiveness of intra-articular hyaluronic acid injection (IAHA) in knee OA patients.

Methods: Medical records of 29 patients with knee OA, who were treated with IAHA injection, were analyzed using a 24 item WOMAC scale for the pain, stiffness, and physical function scores. Furthermore, the patients' quality of life was evaluated based on the SF-12 scale and a global status assessment of knee OA was performed using the Likert scale and visual analogue scale (VAS). The data were analysed statistically.

Results: The overall WOMAC pain, stiffness, and physical function scores decreased following the IAHA administration in patients with knee OA. The mean pain scores decreased from 10.82 to 3.62 and stiffness scores dropped from 4.34 to 2.03. The mean physical function scores decreased from 36.75 to 17.1 ($p < 0.0001$). The Likert scale and VAS demonstrated statistically significant ($P < 0.0001$) improvement in the patient's health status. Overall, nearly 80% of the patients expressed little-to-none physical or emotional problems four weeks after IAHA treatment.

Conclusions: A single IAHA injection provided statistically significant improvement in pain, disability, and quality of life in knee OA patients.

Keywords: Intra-articular hyaluronic acid, Viscosupplementation, Knee osteoarthritis, Non-steroidal anti-inflammatory drugs

INTRODUCTION

A study of community dwelling older adults in India indicated the overall OA prevalence to be 57%, with 33% in rural areas and 60% in urban areas.^{1,2} The community oriented program for the control of rheumatic diseases study estimated the prevalence of knee OA to be 14% and 6% in rural and urban areas of India, respectively.³ The prevalence of knee OA is higher in women and increases with age as well as body mass index (BMI).⁴⁻⁶ India has a rapidly increasing geriatric population, with estimates

showing that the proportion of people aged above 65 years will increase to 19 percent by 2050. The healthcare burden of OA is increasing in India due to a combination of direct costs (hospitalization) and indirect costs (loss of productivity).³ Moreover, knee OA greatly impacts the quality of life of affected patients. In symptomatic knee OA, pain is the predominant symptom contributing to significant physical impairment, sleep disturbance, psychological stress, reduced independence, and poor health perception. Qualitative studies have shown that mood disorders and inability to participate in leisure

activities limited the quality of life of patients with OA.⁷ Radiography is the primary diagnostic aid, as joint space narrowing is a distinct radiological feature of OA.^{8,9} Other cardinal pathogenic processes in OA, such as presence of osteophytes, bone sclerosis, and subchondral cysts, are also detected by radiography.¹⁰⁻¹¹ The limitations of conventional radiography are overcome by using magnetic resonance imaging (MRI) and sonography.¹²

OA management does not entail curative therapy, but there are various treatment modalities that may relieve the pain and disability. The American Academy of Orthopedic Surgeons (AAOS) guidelines for knee OA management include conservative and surgical approaches. The non-pharmacological approach involves lifestyle modifications, education and self-management of OA. In addition, weight loss strategies and muscle-strengthening exercises are advocated to delay the progression of knee OA. Assistive devices such as knee braces, knee sleeves, and foot orthoses may also reduce joint pain.^{8,13} AAOS recommends acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen for patients with symptomatic knee OA. Surgery is indicated for severe knee OA causing significant disability and not responding to conservative therapy.⁸ Both NSAIDs and surgery have significant adverse effects and eligibility concerns.^{3,14-18} Hence, a substantial number of knee OA patients may benefit from novel treatment modalities such as viscosupplementation, which involves intra-articular injection of hyaluronic acid (IAHA).¹⁹ The objective of this prospective interventional study was to assess the clinical effectiveness of IAHA injection therapy, in knee OA patients, by analyzing the patient outcomes and physicians' assessment.

METHODS

Study design and subjects

A pre-post study was conducted in patients treated with IAHA injection for knee OA presented in the Department of Orthopedics, in Amala Institute of Medical Sciences, Amala Nagar, Thrissur, Kerala, India between the periods February 2013 to October 2015. All subjects had radiographic knee OA with Kellgren-Lawrence (K/L) grade 1 to 3 were included. Patients treated with oral or topical or intra-articular steroid one month before the study; patients treated with oral or topical or suppository NSAID within two weeks before the study; patients with secondary knee OA or with OA with a K/L grade ≥ 3 ; patients with rheumatoid arthritis, received joint replacement surgery in either knee or/and a hip; patients who had history of allergies to medicine, systemic or inflammatory joint disease, cancer or other tumor-like intra-articular lesions, hematological, cardiac, hepatic or renal disorders, pregnancy or lactation were excluded from the study. The study design was approved by the

Institutional Research Ethics Committee and conducted according to the standards of declarations of Helsinki.

Treatment procedure

Patients in supine position under the local anesthesia and strict aseptic precaution a single intra-articular injection (60 mg in 3 ml, Durolane®) was given by the lateral parapatellar approach. After the injection, the patient was asked to flex and extend the knee 10-15 times. Patients were discharged on the same day with 3 day prescription of antibiotic, cefuroxime (500 mg, bd for 3 days). The clinical outcome was measured after 4 weeks and analyzed statistically.

Measurement of clinical outcome

The center recorded patients' pain and stiffness scores on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale at baseline and four weeks.²⁰ The WOMAC scale contains 24 items as three subscales: (1) pain (five items): during walking, using stairs, in bed, sitting or lying, and standing; (2) stiffness (two items): after first waking and later in the day; (3) physical function (17 items): stair use, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on/taking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, and light household duties. The WOMAC scale was developed for knee and/or hip OA patients and is also available in five-point Likert scale and 100 mm visual analog scale (VAS) formats.²⁰ The outcome variables in this study included improvement in WOMAC pain, stiffness and physical function scores as well as patient's assessment of quality of life using the SF-12 scale.

Statistical analysis

Statistical analysis was performed using the SPSS (v16, IBM, CA, USA). Descriptive statistics were used to represent the numerical and categorical data. Inferential statistics were derived from the paired t-test at a 5% level of significance ($p < 0.05$).

RESULTS

Patient profile

Patients involved were aged 34–82 years and had a BMI range of 20–30 (25 ± 4), while systolic and diastolic blood pressure ranges were 100–180 (136 ± 24) mmHg and 70–120 (86 ± 14) mmHg, respectively. Of the total patient population ($n=29$), 15 were female and majority of the patients were non-smokers (21%, $n=21$). Among the patients with unilateral knee OA (59%, $n=17$), OA in the right knee was more common (59%, $n=10/17$) than in the left knee (41%, $n=7/17$). The mean duration of OA at the time of IAHA treatment was 48 ± 30 months (Table 1).

Concomitant therapies used were antidiabetic agents, antihypertensives and antihyperlipidemics. Physical examination results of participating patients show that IAHA injection decreased pain and swelling in a

significant number of patients (Table 2). After four weeks, pain was reported by 17% patients (versus 97% at baseline) and swelling by 10% (versus 59% at baseline).

Table 1: Demographics and baseline characteristics of knee OA patients (n=29).

| Patient population | Mean±SD or n (%) |
|---|------------------|
| Age (years) | 58±12 |
| Female gender | 15 (52%) |
| Body mass index (BMI; kg/m ²) | 25±4 |
| Systolic blood pressure (mmHg) | 136±24 |
| Diastolic blood pressure (mmHg) | 86±14 |
| Ex-smoker | 6 (21%) |
| Non-smoker | 21 (72%) |
| Duration of symptomatic knee OA (months) | 48±30 |
| Unilateral knee OA | 17 (59%) |
| Right knee OA | 10 (59%) |
| Left knee OA | 7 (41%) |

Table 2: Physical examination at baseline and at four weeks after IAHA treatment.

| Physical examination | At baseline n (%) | At four weeks (%) |
|----------------------|-------------------|-------------------|
| Pain | 28 (97%) | 5 (17%) |
| Swelling | 17 (59%) | 3 (10%) |

Table 3: WOMAC pain scores at baseline and after four weeks.

| WOMAC pain score | Baseline | After four weeks |
|---|------------|------------------|
| While walking on a flat surface | 2.41±0.77 | 0.79±0.88 |
| While going up or down the stairs | 3.06±0.59 | 1.37±0.71 |
| At night, while in bed (i.e., pain that disturbs sleep) | 2.06±1.16 | 0.44±0.67 |
| While sitting or lying down | 1.41±1.18 | 0.41±0.67 |
| While standing | 1.86±0.91 | 0.58±0.61 |
| Total pain score | 10.82±3.77 | 3.62±2.99* |

Values are Mean ± SD. N= 29, * p<0.0001

Table 4: WOMAC stiffness scores at baseline and after four weeks.

| WOMAC stiffness score | Baseline | After four weeks |
|---|-----------|------------------|
| How severe has your stiffness been after you first woke up in the morning? | 2.31±1.07 | 1.1±0.3 |
| How severe has your stiffness been after sitting or lying down or while resting later in the day? | 2.03±1.01 | 0.79±0.49 |
| Total pain score | 4.34±1.95 | 2.03±0.82* |

Values are Mean ± SD. N= 29, * p<0.0001

WOMAC scores

The WOMAC pain scores for various daily movements such as walking, climbing stairs, sitting, standing, and lying down improved significantly (Table 3). At baseline, the highest mean pain score of 3.06 was reported for going up or down the stairs, which reduced significantly to a mean pain score of 1.37. The decrease in total pain scores from baseline (10.82±3.77) to four-week follow-up (3.62±2.99) was statistically significant (p<0.0001) (Table 1).

Similarly, improvements in mean stiffness scores were recorded four weeks after IAHA treatment. The decrease in total stiffness scores from baseline (4.34±1.95) to four-week follow-up (2.03±0.82) was statistically significant (p<0.0001) (Table 4).

A comprehensive assessment of the physical function scores demonstrated that four weeks after IAHA treatment, knee OA patients reported improvements in all recorded daily activities (Table 5). Most noticeable changes – a drop of over 1 point per activity – were

recorded for performing household chores, wearing or removing socks/stockings/pantyhose, getting in/out of a vehicle, and using the bathtub/toilet. The largest change from 2.28 to 0.72 was recorded for performing light

household chores. The decrease in total physical function scores from baseline (36.75 ± 12.79) to four-week follow-up (17.1 ± 10.75) was statistically significant ($p < 0.0001$).

Table 5: WOMAC physical function scores at baseline and after four weeks.

| WOMAC physical function score | Baseline | | After four weeks | |
|--|--------------|--------------|------------------|---------------|
| | Mean | SD | Mean | SD |
| While going down the stairs | 2.65 | 0.72 | 1.31 | 0.6 |
| While going up the stairs | 2.79 | 0.94 | 1.44 | 0.68 |
| While getting up from a sitting position | 2.17 | 0.92 | 0.93 | 0.65 |
| While standing | 1.79 | 0.9 | 0.55 | 0.5 |
| While bending to the floor | 2.13 | 0.78 | 1 | 0.75 |
| While walking on a flat surface | 2 | 1 | 0.89 | 0.91 |
| Getting in or out of a car or bus | 2.41 | 0.73 | 1.31 | 0.66 |
| While going shopping | 2.03 | 1.01 | 1.2 | 0.72 |
| While putting on socks, panty hose, or stockings | 2.1 | 1.01 | 1.03 | 0.86 |
| While getting out of bed | 1.82 | 1 | 0.93 | 0.84 |
| While taking off socks, panty hose, or stockings | 2.03 | 0.94 | 1.03 | 0.86 |
| While lying in bed | 1.51 | 1.24 | 1.1375 | 1.24 |
| While getting in or out of the bathtub | 2.1 | 0.81 | 1 | 0.54 |
| While sitting | 1.58 | 1.11 | 0.72 | 0.79 |
| While getting on or off the toilet | 2.34 | 0.79 | 1.1 | 0.97 |
| While doing heavy household chores | 2.89 | 0.77 | 1.55 | 0.86 |
| While doing light household chores | 2.28 | 0.85 | 0.72 | 0.84 |
| Total physical function score | 36.75 | 12.79 | 17.1 | 10.75* |

Values are Mean \pm SD. N= 29, * $p < 0.0001$

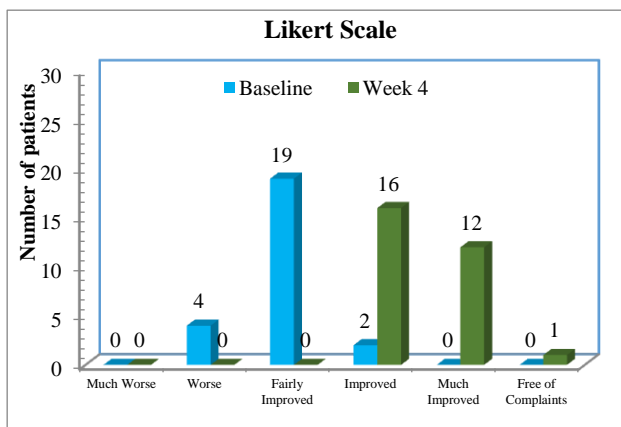


Figure 1: Global status assessment of knee OA using the Likert scale.

Global assessment of treated knee and quality of life

A global status assessment of knee OA was performed using the Likert scale and VAS (Figure 1). As per the Likert scale, a majority of the patients reported improved (55%, $n=16/29$) and much improved (41%, $n=12/29$) status (Figure 1) four weeks after IAHA treatment. Similarly, as per VAS, a majority of the patients reported feeling “well” (76%, $n=22/29$) four weeks after IAHA treatment. However, five patients had an overall status of “little well” and one had a “poor” status (Figure 2). A

significant number of patients reported a positive change in health status from fair/poor at baseline (62%, $n=18/29$) to good (31%, $n=9/29$) and excellent at follow-up (59%, $n=17$). There was an improvement in the sense of accomplishment and reduction in work/activity limitations. However, most patients still felt limited in terms of performing moderate activities and climbing stairs. After IAHA treatment, more number of patients reported feeling calmer, more energetic and fewer of them had physical/emotional problems (Table 6).

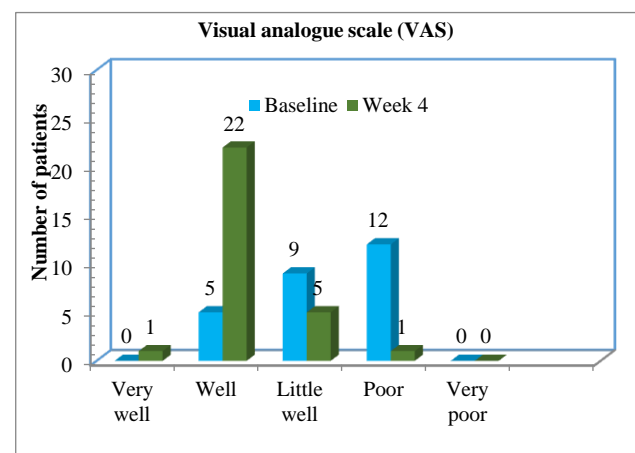


Figure 2: Global status assessment of knee OA using VAS.

Table 6: Quality of life at baseline and after four weeks.

| Quality of life | Baseline (%) | After four weeks (%) |
|--|--------------|----------------------|
| Question 1: Health status | | |
| Excellent | 4 (13.80) | 9 (31.03) |
| Good | 7 (24.14) | 17 (58.62) |
| Fair/Poor | 18 (62.06) | 3 (10.35) |
| Question 2a: Moderate activities | | |
| Yes, limited a lot/a little | 29 (100) | 28 (96.55) |
| No, not limited at all | 0 | 1 (3.45) |
| Question 2b: Climbing status | | |
| Yes, limited a lot/a little | 29 (100) | 28 (96.55) |
| No, not limited at all | 0 | 1 (3.45) |
| Question 3a: Less accomplishment | | |
| All/Most of the time | 21 (72.41) | 3 (10.35) |
| Some of the time | 6 (20.69) | 7 (24.14) |
| A little/none of the time | 2 (6.90) | 19 (65.51) |
| Question 3b: Limited in the kind of work or other activities | | |
| All/Most of the time | 22 (75.86) | 2 (6.90) |
| Some of the time | 5 (17.24) | 3 (10.35) |
| A little/none of the time | 2 (6.90) | 20 (68.97) |
| Missing | 0 | 4 (13.79) |
| Question 4: Pain interfere in last four weeks | | |
| Not at all/a little bit | 0 | 26 (89.65) |
| Moderately | 8 (27.59) | 1 (3.45) |
| Quite a bit/extremely | 21 (72.41) | 2 (6.90) |
| Question 5a: Did work or other daily activity (less accomplished) | | |
| All/Most of the time | 6 (20.69) | 2 (6.90) |
| Some of the time | 18 (62.06) | 7 (24.14) |
| A little/none of the time | 3 (10.35) | 20 (68.96) |
| Missing | 2 (6.90) | 0 |
| Question 5b: Did work or other daily activities (less carefully than usual) | | |
| All/Most of the time | 6 (20.69) | 4 (13.80) |
| Some of the time | 17 (58.62) | 7 (24.14) |
| A little/none of the time | 6 (20.69) | 18 (62.06) |
| Question 6a: Feeling calm and peaceful | | |
| All/Most of the time | 6 (20.69) | 2 (6.90) |
| Some of the time | 12 (41.37) | 7 (24.14) |
| A little/none of the time | 11 (37.94) | 20 (68.96) |
| Question 6b: Feeling energetic | | |
| All/Most of the time | 3 (10.35) | 24 (82.75) |
| Some of the time | 17 (58.62) | 3 (10.35) |
| A little/none of the time | 9 (31.03) | 2 (6.90) |
| Question 6c: Feeling Downhearted and Low | | |
| All/Most of the Time | 15(51.73) | 3(10.35) |
| Some of the Time | 5(17.24) | 26(89.65) |
| A Little/None of the Time | 9(31.03) | 0 |
| Question 7: Physical health or emotional problems | | |
| All/Most of the time | 19 (65.52) | 2 (6.90) |
| Some of the time | 10 (34.48) | 4 (13.79) |
| A little/none of the time | 0 | 23 (79.31) |

DISCUSSION

The main challenges in the management of knee OA include the lack of local consensus guidelines for

promoting evidence-based practice and the clinicians' preference for surgery over conservative treatment for managing knee OA patients.²¹ Long-term treatment with NSAIDs increases the risk of adverse events and surgery

is linked to several eligibility, safety, and affordability concerns.^{3,14-18} Viscosupplementation or IAHA injections are used to restore the viscoelasticity of the synovial fluid and the natural protective function of the joint in knee OA.²²

In this retrospective study, we examined medical records of knee OA patients who were treated with one injection of a high molecular weight gel of HA produced from a non-animal source.²³ The potential mechanisms of action of IAHA include chondroprotection, HA synthesis, anti-inflammatory effect, and analgesic effect. At the molecular level, IAHA binds with CD44 receptors and mechano-sensitive ion channels to disrupt their downstream cytokine-mediated signaling pathways which could render the anti-inflammatory effect.²⁴

In our study, baseline physical examination revealed pain in nearly all (97%) and swelling in over half (59%) of the patients with knee OA. Post-IAHA injection follow-up after four weeks found no pain and swelling in nearly 72% and 79% of the patients, respectively. McGrath *et al* reported a study in which a single injection of IAHA significantly reduced knee pain VAS scores in knee OA patients for more than 6 months.²³ OA is characterized by the slow degradation of the cartilage, accompanied by pain and progressive disability.²⁵ In our study, a single dose of IAHA, at the four-week post-treatment time point, significantly reduced WOMAC pain, stiffness, and physical function scores ($p < 0.0001$). OA greatly impacts a patient's daily life including work productivity, social activities, relationships, body image, and emotional well-being.²⁵ We employed the Likert scale and VAS to conduct a global assessment of disease status among the participating knee OA patients. Our analysis shows that IAHA treatment significantly improved the overall health status of knee OA patients. In addition, a quality for life questionnaire evaluated the impact of IAHA treatment on the patient's emotional and mental status. Significantly more number of patients reported feeling a better sense of accomplishment, less restricted, calmer, and energetic. Overall, nearly 80% of the patients expressed little-to-none physical or emotional problems four weeks after IAHA treatment. Previously IAHA has been shown to improve the physical component but not the mental component of the short Form 36 version 2 (SF-36 V2) medical outcome questionnaire.²³

Our analysis of IAHA treatment is in-line with previously reported effects of IAHAs in knee OA management. Meta-analyses of IAHA in the management of knee OA reveal that IAHA has higher efficacy than NSAIDs and other pain relievers and reduces the incidence of total knee replacement surgery.^{26,27}

An ideal knee OA patient for whom viscosupplementation is an effective treatment choice is one who does not respond well to conservative treatment, has comorbidities, or is ineligible for surgery.^[28] Viscosupplementation is a treatment option based on the

physiological properties of shock absorption, traumatic energy dissipation, ability to form a protective coating on the articular cartilage surface, and lubrication.²² Both the US FDA and EU have approved several viscosupplements for treating knee OA.^{28,29} This study has a few limitations such as small sample size, lack of long-term follow-up, limited safety data. The results of this study need to be replicated in a larger patient population for longer time intervals with appropriate documentation of safety and concomitant medications.

CONCLUSION

The overall WOMAC pain, stiffness, and physical function scores decreased following IAHA administration in patients with knee OA. A global status assessment using the Likert scale and visual analogue scales demonstrated statistically significant improvement in the patient's health status. Overall, nearly 80% of the patients expressed little-to-none physical or emotional problems four weeks after IAHA treatment, from baseline to 4-week follow-up.

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