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Research Article

SAFETY AND EFFICACY OF INTRA-ARTICULAR STEROID INJECTIONS IN OSTEOARTHRITIS OF THE KNEE − A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: The objective of the study was to assess the safety and efficacy of intra-articular steroid injections in osteoarthritis of knee.

Methods: This prospective observational study was conducted for a period of 12 months in a tertiary care hospital. Patients were given intra-articular injections of triamcinolone hexacetonide 40 mg (1 cc) in the affected knee at the time of enrollment and thereafter at 6 and 12 weeks. The treatment response was evaluated based on the improvement in the various clinical scoring systems. Comparison of quantitative variables of successive follow-up with baseline value was analyzed. $p < 0.05$ was taken as level of significance.

Results: Of the 106 patients included in the study, the mean age was 64.12±8.69 years. The mean 50 foot walking time improved from 13.85 s to 12.64 s (p=0.003) by 24 weeks. Range of motion improved from a mean of 126.75–131.63° (p=0.001). The physician's global assessment score improved from a baseline mean of 54.42–46.39 while the patient's global assessment score progressed from 57.8 to 46.38 both being statistically significant. Patient's pain assessment score reduced from baseline mean value of 57.32–45.95 and nocturnal pain improved to 30.24 at 24 weeks from a baseline value of 36.51. The mean Western Ontario and McMaster Universities Osteoarthritis Index score improved to 45.93 from baseline of 56.92.

Conclusion: Repetitive IA steroid injections appear to be safe with no significant deleterious effects on the anatomical joint structure.

Keywords: Osteoarthritis, Intra-articular, Corticosteroids, WOMAC score, Kellgren-Lawrence scale, Knee range of motion, Triamcinolone acetate.

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INTRODUCTION

Osteoarthritis (OA) is by far the most common type of arthritis and the major cause of disability in people older than 50 years [1,2]. Knee is the most affected joint followed by the hip and the hand joints [2,3]. As per the Global Burden of Disease 2000 study, published in the World Health Report 2002, OA is the 4th leading cause of Years Lost to Disability (YLDs) at the global level, which contributes to 3.0% of total global YLDs.

The prevalence of osteoarthritis increases with age and contributes to an increasing burden on health care among the aging population [4]. In India, the prevalence of the disease in the adult rural population is estimated to be 5.8%. Although more cases are reported in men, the incidence in women rises after menopause, and by age of 65, the prevalence is twice as high in women as in men [4]. The risk of developing OA is determined by both systemic and local factors such as obesity and metabolic diseases, age, sex, ethnicity and race, genetics, nutrition, smoking, bone density, and muscle function.

No specific therapy has yet been clearly shown to prevent the progression of osteoarthritis. Treatment options ranges from simple advice about modifying activity to joint replacement. Pain management includes use of simple analgesics and if not adequately a nonsteroidal anti-inflammatory drug (NSAID) can be used. Concerned about the possible side effects of long-term selective and non-selective NSAIDs, intra-articular treatment options are being considered. Intra-articular corticosteroids have considerable value when used appropriately and judiciously [1,2].

OA is a complex interaction of degradation and repair of the cartilage, bone, and synovium with secondary components of inflammation. Chondrocytes from OA patients have been shown to be deficient in glucocorticoid receptors with decreased response to circulating glucocorticoids. This may be one of the contributing factors for the increased synthesis of cytokine and metalloproteinase in the degrading cartilage. Intra-articular steroids by inhibiting the synthesis of cytokines and metalloproteinase not only provide symptomatic relief but also reduce the severity of cartilage lesions and the size of osteophytes [2,5].

As per the American College of Rheumatology treatment guidelines, intra-articular steroid is a part of management of knee OA [6]. It is found to be more effective in knee osteoarthritis associated with synovitis and effusion. Steroid injections may be given up to 3–4 times per year. The rate of absorption and the duration of action are related to the solubility of the compound injected. Triamcinolone hexacetonide is the least water-soluble preparation currently available [7].

The fear that long-term use of these injections could promote joint destruction and tissue atrophy has made its use controversial [8]. Conversely, studies both *in vitro* and *in vivo* in experimental models have shown that corticosteroid injections can, in fact, reduce progression of structural changes [7,9]. Very few studies have been conducted in India assessing the safety and efficacy of IA injections in osteoarthritis knee, and hence, this study is significant in the current setting.

METHODS

This prospective observational study was conducted for a period of 12 months, from April 2014 to March 2015, among the patients attending the outpatient clinic of the Department of Physical Medicine and Rehabilitation, Government Medical College, a tertiary care hospital in Thiruvananthapuram. The study was approved by the Institutional Ethics Committee (IEC). All participants were informed about the study and written consent was obtained. Sample size of 99 was determined by the data obtained from a similar study.

Inclusion criteria

All patients between 30 and 80 years of age diagnosed with knee OA as per ACR criteria, with radiological evidence of OA within 6 months of start of the study, with radiographic severity of 2–3 on the Kellgren/Lawrence scale for joint space narrowing, osteophytes, or sclerosis and those not responding adequately to traditional nonsteroidal anti-inflammatory drug (NSAID).

Exclusion criteria

Unwilling patients, patients with chondrocalcinosis, isolated patellofemoral OA, or any other secondary conditions (including inflammation, sepsis, metabolic abnormalities, and trauma) were excluded from the study, or if they had acute or chronic infection (including tuberculosis). Patients with radiologic Grade 4 OA (Kellgren/Lawrence scale) or who are candidates for imminent knee joint surgery were also excluded from the study. The study also excluded patients who received intra-articular corticosteroids injection in the study knee within the previous 6 months.

A common standardized format was used for data collection from the selected candidates. The study was carried out in five visits. In the first visit, detailed history, including history and medication history, was taken along with a thorough general and systemic examination. Baseline assessment was done using WOMAC VA 3.0 score, 50-foot walking time, knee range of motion in degrees, physicians global assessment using VAS, patients global assessment using VAS, patient's pain assessment using VAS, patient's nocturnal pain assessment using VAS, and Kellgren-Lawrence scale. Baseline investigations such as complete blood cell count, random blood sugar, erythrocyte sedimentation rate, rheumatoid factor, serum creatinine, alkaline phosphatase, serum calcium, and phosphorus were also recorded.

Patients were given intra-articular injections of triamcinolone hexacetonide 40 mg (1 cc) in the affected knee at the time of enrollment and thereafter at 6 weeks and 12 weeks. A total of not more than 3 doses were given to the patients. Patients were withdrawn from the study if a severe reaction to the injections occurred, or if there was evidence of an active infection in the injected joint at any time during the study (however, there were none in this study group). Patients underwent clinical evaluation at baseline and every 6 weeks thereafter, for the duration of 6 months (at 6 weeks, 12 weeks, 18 weeks, and 24 weeks).

Patients were evaluated for the treatment response at each visit using the parameters for treatment response being WOMAC score, 50-foot walk test, and knee range of motion and reduction in pain intensity using VAS. The safety profile was assessed in terms of the adverse effects observed by the physician or reported by the patients at each visit and also by the radiological progression of the disease graded by the Kellgren-Lawrence scale, which was done at 6 and 24 weeks.

Patients were permitted to receive simple analgesics and non-pharmacological modalities including footwear modification, as per physician's advice, following the clinical practice guidelines.

Statistical analysis

SPSS V.16 was used for the data analysis. Quantitative variables were described by mean and standard deviation. Qualitative variables were expressed in terms of frequency distribution. Comparison of quantitative variables between the two groups was analyzed with t-test, whereas the quantitative variables among more than 2 groups were analyzed by ANOVA test. Comparison of quantitative variables of successive follow-up with baseline value was analyzed by repeated measure ANOVA with multiple comparisons. $p<0.05$ was taken as level of significance.

RESULTS

A total of 106 patients who met the inclusion criteria were included in the study. The mean age of the study population was 64.12±8.69 years of which 39.6% of them belonged to the age group of 61–70 years (Fig. 1). The study showed a predominance of female population, accounting for 66% (Fig. 2). The mean weight and BMI at baseline were 68.26 kg and 26.46 kg/m^2, respectively (Table 1 and Fig. 3).

Duration of illness ranged from 1.5 years to 12 years, with mean being 7.54 years. Mean hemoglobin of the group was 11.37±1.4 gm/dL, ESR ranged from 3 to 54 mm with a mean of 33.33. Serum creatinine ranged from 0.5 to 1.5 mg/dl. Alkaline phosphatase in the study population ranged from 46 to 154 IU/L, with a mean of 89.11. Mean serum calcium level was 9.88±0.83 mg/dL (Table 2). About 30.2% of the study population were diabetic, and in our study, there was no statistically significant difference in the treatment outcome between diabetics and non-diabetics (Fig. 4). Among the 106 patients, 51.9% of patients did not need additional NSAIDs for symptom relief during the study period and there was no statistically significant difference in the treatment outcome between patients who received NSAIDs and those who did not (Fig. 5).

50-foot walking time

At baseline, the mean 50-foot walking time was 13.85 s with reduction at 24 weeks to 12.64 s (p=0.003) (Table 3).

Knee range of motion

Range of motion had a significant improvement from a mean of 126.75° at baseline to 131.63° at 24 weeks (p=0.001) (Table 4).

Global assessment of the disease activity scored with the VAS scale

On a scale ranging from 0 to 100, the physicians global assessment score improved from a baseline mean of 54.42–46.39 (p=0.007) (Fig. 6) while the patient's global assessment score progressed from a baseline mean of 57.8–46.38 both being statistically significant improvement (p=0.04) (Fig. 7).

Patient's assessment of pain, 100 mm VAS

Patient's pain assessment score gradually reduced from baseline mean value of 57.32–45.95 at 24 weeks (p=0.002) (Fig. 8) and nocturnal pain gradually improved to 30.24 at 24 weeks (p=0.011) from a baseline mean value of 36.51 (Fig. 9).

WOMAC score

The mean score at baseline was 56.92, which markedly improved to 45.93 by 24 weeks (p=0.007). The difference was statistically significant suggesting a positive response to intra-articular steroid therapy (Fig. 10).

Kellgren-Lawrence scale

At baseline, 58 patients (54.7%) belonged to Stage II, while 48 patients (45.3%) belonged to Stage III. While neither of patients showed downstaging of their radiological disease during the study period, none progressed to Stage IV as well (Fig. 11).

DISCUSSION

Osteoarthritis of the knee is one of the most frequent forms of arthritis, especially in elderly population, and is a major cause of pain and disability. Intra-articular (IA) corticosteroid injections have been in use in clinical practice for decades for pain relief and control of local inflammation in OA [10-12]. The demographic profile of our study group revealed a predominance of elderly and female population which correlated with a study by Raynauld *et al*. [13]. The mean weight and BMI of the patients showed a gradual sustained reduction to 68.06 kg which was comparable with the results observed in a similar study by Beyaz *et al*. [14]. This weight reduction strategy has paid rich dividends in attaining good response to intra-articular steroids.

ACR guidelines propagate the use of NSAIDs for symptom relief [6] and hence were prescribed on a need to need basis in the present study. However, on analysis, it was found that the treatment response to intra-articular steroids was independent of NSAID usage. The role of diabetes mellitus in the natural course of osteoarthritis is still a matter of debate with some studies supporting a causative role while some others giving evidence to the contrary [15-17]. Our study found that treatment response was independent of patient's diabetic status.

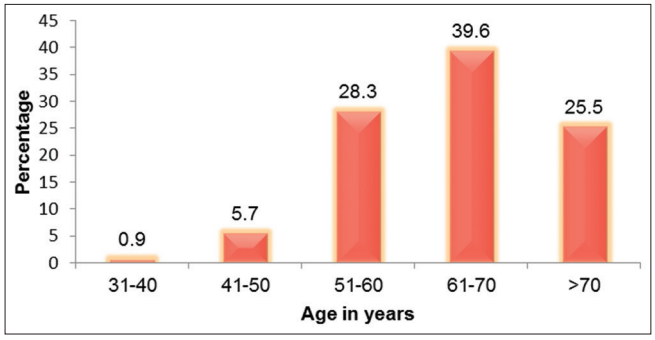

Fig. 1: Age distribution of the patients receiving intra-articular steroids

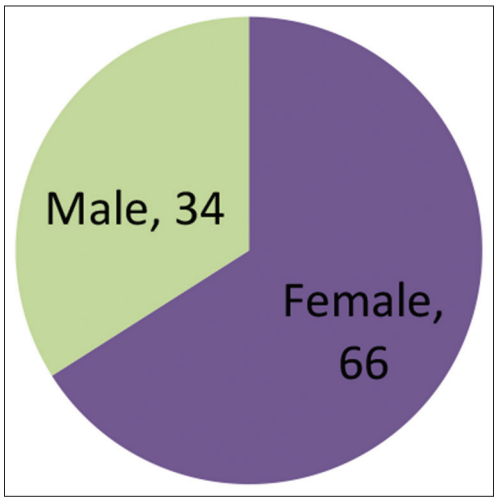

Fig. 2: Sex distribution of the patients receiving intra-articular steroids

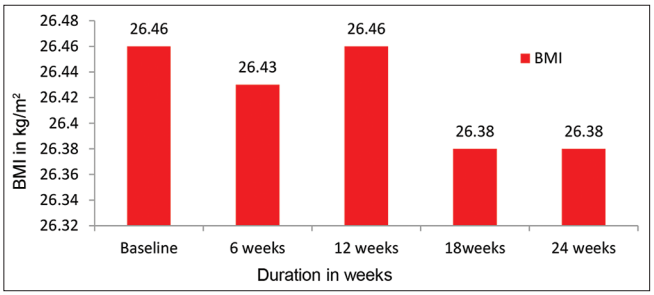

Fig. 3: Comparison of BMI in patients receiving intra-articular steroids

Several well-accepted outcome measurement variables were employed in our study to assess response [18,19]. All the variables used showed good improvement from both the patient and physician's point of view. A 50-foot walking time, a well-known marker for assessing treatment response, showed a statistically significant improvement, which was comparable with the results observed in a similar study by Raynauld *et al*. [13]. Range of motion around knee joint showed a significant improvement thereby affording symptomatic relief, including pain and stiffness. In a similar study by Dieppe *et al.,* the best improved parameter was knee ROM [1].

The WOMAC score is a standard scale to assess the treatment response and is used as self-report measures of lower extremity symptoms and function [20,21]. Progressively improving trend was found in patients receiving intra-articular steroids and is comparable to the results in a similar study by Valtonen *et al*. [7].

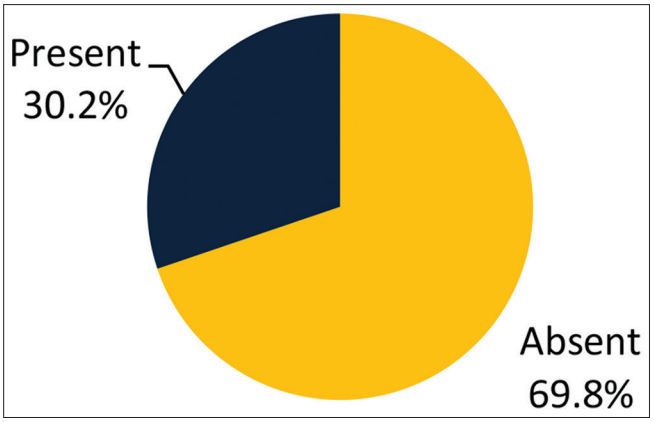

Fig. 4: Diabetic status of the patients receiving intra-articular steroids

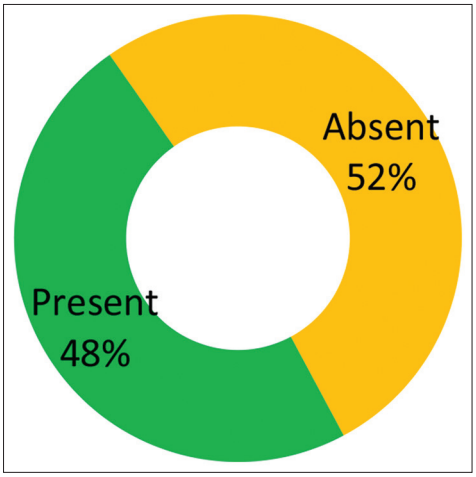

Fig. 5: NSAID use among patients receiving intra-articular steroids

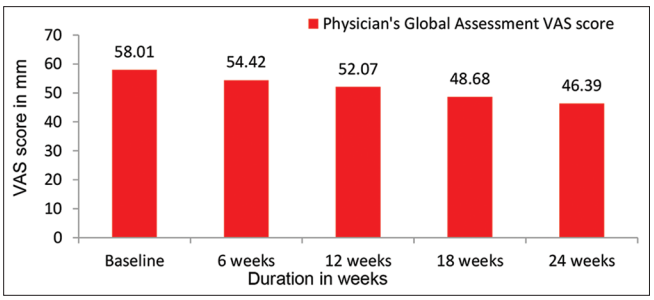

Fig. 6: Comparison of physician's global assessment score in patients receiving intra-articular steroids

The global assessment of the disease activity score with the VAS scale is a valuable quantitative measure to follow the course of the disease and to monitor the effectiveness of therapeutic interventions [22,23]. In the present study, both the physician's and patient's assessment scores showed a statistically significant improvement. Contradictory findings were observed in a study by Raynauld *et al.* wherein intra-articular steroids failed to show improvement in the global assessment scores [7]. The small differences between this data and the Western data could be due to the ethnic differences and needs to be evaluated with tools available in the emerging horizon of pharmacogenomics.

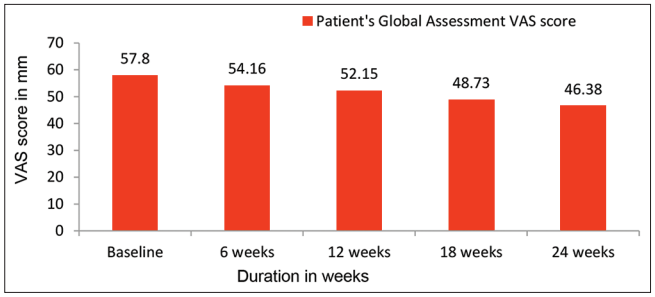

Fig. 7: Comparison of patient's global assessment score in patients receiving intra-articular steroids

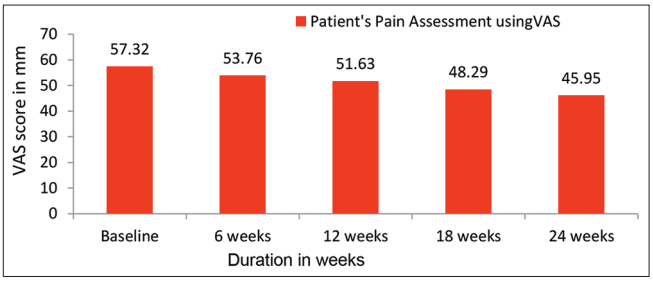

Fig. 8: Comparison of patient's pain assessment using VAS

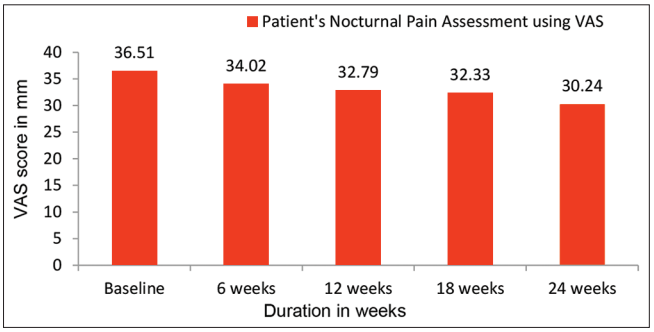

Fig. 9: Comparison of patient's nocturnal pain assessment using VAS

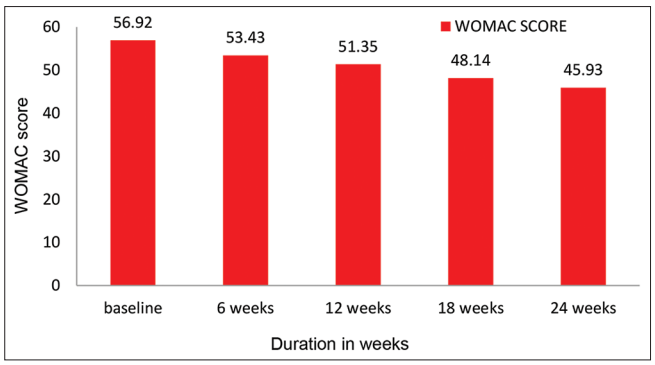

Fig. 10: Comparison of WOMAC score in patients receiving intra-articular steroids

The VAS scale was used to make a subjective judgment of the patient's disease activity based on the patient's symptoms like pain around the knee joint and the episodes of nocturnal pain [19]. In this study, the patient's pain VAS score showed significant reduction which was concurrent with the finding in a similar study by Beyaz *et al.* [14].

Toxicity profile was evaluated based on the radiological progression of the disease as per the Kellgren-Lawrence scale and the adverse effects reported by the patients or observed by the physicians [24]. During the study period, no radiological progression was documented among the included patients a per the Kellgren-Lawrence grading system. While neither of patients showed downstaging of their radiological disease during the study period, none progressed to Stage IV as well. Similar findings were reported in a study by Raynauld *et al.* [13]. Treatment with intra-articular steroids was effective in halting the disease progression to a certain extent, which in itself proves the safety of this mode of treatment.

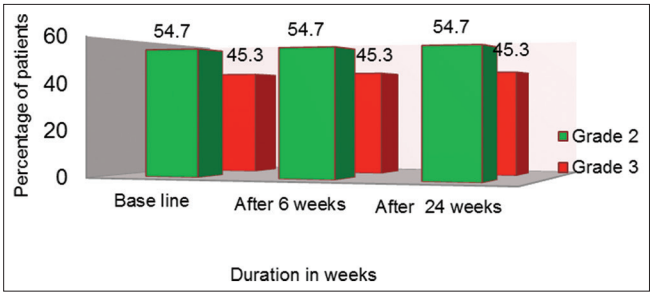

Fig. 11: Radiological grading using Kellgren-Lawrence scale

Table 1: Weight distribution of the patients receiving intra-articular steroids

Weight in kg	Mean	SD	p value
Baseline	68.26	7.76	
At 6 weeks	68.18	7.66	0.095
At 12 weeks	68.25	7.64	0.779
At 18 weeks	68.06	7.84	0.020
At 24 weeks	68.06	7.60	0.034

Table 2: Baseline characteristics of the patients receiving intra-articular steroids

Baseline characteristics	Minimum	Maximum	Mean	SD
Age (in years)	38	80	64.12	8.69
Duration (in years)	1.5	12.0	7.54	2.46
Height (in cm)	149	180	160.80	7.00
Hemoglobin (in gm/dL)	8.5	14.5	11.37	1.40
Total count (per cmm)	4500	11,200	7282.1	1589.3
ESR (in mm)	3	54	33.33	16.01
RBS (in mg/dL)	54	212	116.28	37.74
Serum creatinine (in mg/dL)	0.5	1.5	0.93	0.28
ALP (in IU/L)	46	154	89.11	24.52
Calcium (in mg/dL)	8.5	11.4	9.88	0.83
Phosphorus (in mg/dL)	2.5	4.2	3.63	0.45

Table 3: Comparison of 50-foot walking time

50-foot walking time (in seconds)	Mean	SD	p value
Baseline	13.85	1.83	
After 6 weeks	13.53	1.78	0.087
After 12 weeks	13.31	1.70	0.074
After 18 weeks	12.92	1.72	0.005
After 24 weeks	12.64	1.81	0.003

Table 4: Comparison of knee range of motion in patients receiving intra-articular steroids

Knee ROM (in degrees)	Mean	SD	p value
Baseline	126.75	8.13	
At 6 weeks	128.25	8.16	0.041
At 12 weeks	129.25	8.50	0.040
At 18 weeks	130.01	8.13	0.005
At 24 weeks	131.63	7.61	0.001

A study by Beyaz *et al*. showed that none of the patients suffered from any significant adverse effects [14]. Similar result was obtained in our study as well, which can be accounted by careful patient selection, proper injection technique and management protocols, and good patient acceptability. The intra-articular route, while minimizing the innumerable side effects of systemic steroids, also allows adequate drug concentration in the joint space, leading to optimum anti-inflammatory activity.

Our findings expand and enhance observations made in previous short-term studies in which a strong trend toward greater clinical improvement in the IA steroid group was shown, this difference being statistically significant for key variables such as knee pain and stiffness [1,13,14,20].

Limitations of the study

The present study was a prospective observational single-arm study. A randomized controlled trial with a comparator group would have given a better outcome. The long-term side effects of intra-articular steroids could be missed out due to the short-term study. The radiological progression of the disease could be assessed by more accurate grading techniques like digital fluoroscopy-assisted joint width measurement, which is more sensitive in reflecting the disease progression than the Kellgren-Lawrence scale used in the present study.

CONCLUSION

The present study was done to assess the treatment response and the toxicity profile of intra-articular steroids. The finding suggests that repetitive IA steroid injections appear to be safe with no significant deleterious effects of the steroids on the anatomical joint structure. Moreover, the use of IA injections of triamcinolone hexacetonide afforded relief of some of the symptoms of knee OA, including pain and stiffness, thereby improving the quality of life.

AUTHORS' CONTRIBUTIONS

All authors have contributed critically to the preparation of the manuscript.

CONFLICTS OF INTEREST

No potential conflicts of interests were disclosed.

AUTHORS' FUNDING

Nil.

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