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Original Research Article

Comparative analysis of efficacy and tolerability of tramadol versus diclofenac in treatment of knee osteoarthritis

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ABSTRACT

Background: Present study was conducted on patients of osteoarthritis (OA) treated with the traditional drug diclofenac sodium and compares it with tramadol, with the primary objective for determining effectiveness and tolerability based on WOMAC scores.
Methods: The study was conducted as a randomized clinical study of the effectiveness and tolerability of tramadol versus diclofenac in the treatment of knee OA, at Tertiary care institute of Gujarat in the department of orthopedics. Consecutive patients were allotted serially in two groups; tramadol group (n=75) One tablet orally twice daily for 8 weeks. Diclofenac group (n75) patients received 75 mg oral dose of diclofenac 2 times daily for a period of 8 weeks. Overall improvement was evaluated through various parameters.
Results: About 33% decrease in the scoring of stiffness domain of the WOMAC OA index questionnaire in the tramadol group and a 21% decline in the diclofenac group was observed. There was a 65% decrease in the scoring of knee joint tenderness questionnaire in the tramadol group and a 44% reduction in the diclofenac group. Tramadol was found to be more effective in improving the WOMAC OA index. WOMAC score (overall) and knee joint tenderness scores were also improved by tramadol than diclofenac.
Conclusions: There was a significant improvement in the standard of life in patients suffering from knee OA when treated with tramadol. Tolerability was better with tramadol than diclofenac.

Keywords: Diclofenac, Knee joint, Osteoarthritis, Tramadol

INTRODUCTION

Osteoarthritis (OA) is a chronic, inflammatory joint disease in the whole world.[1] In India, more than 20% of the total population is suffering from arthritis; although the chief cause of the disease is unknown, morphological changes witnessed in OA include cartilage erosion as well as inflammation.[2] The most affected joints include the hips, knees, back and neck, joints of the fingers, the base of the thumb, and big toe.[3] OA is more common in women than in men. The worldwide estimates are that 9.6% of men and 18% of women aged more than 60 years have symptomatic OA.[4]

Risk factors for OA include advanced age, female gender, genetic predisposition, obesity, and joint injury including trauma, repetitive use, and prior inflammation.[5-8] Genes that encode collagen type II have been proposed as candidate genes for familial OA.[9, 10] Radiographs can help confirm OA when the diagnosis is uncertain from clinical examination. It is usually not difficult to differentiate OA from a systemic rheumatic disease, such as rheumatoid arthritis, because joint involvement in the latter disease is usually symmetric and polyarticular, with arthritis in wrists and metatarsophalangeal joints and constitutional features such as prolonged morning stiffness, fatigue, weight loss, or fever may be seen.[11] Synovial fluid analysis

reveals mild leukocytosis is i.e., with a predominance of mononuclear cells. Synovial fluid analysis is of particular value in excluding other conditions, such as calcium pyrophosphate dehydrates deposition disease, gout or septic arthritis.[12]

The main oral pharmacological options currently used to treat pain caused by OA include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates.[13] Recently, the international osteoarthritis research society (OARSI) has published a series of recommendations based on review of available guidelines for the management of patients with OA of the hip and knees.[14] They recommend taking the lowest effective dose of NSAIDs, avoiding long-term use, as they are associated with dose and duration-related risks of gastrointestinal, cardiovascular, and renal-function adverse events (AEs). They also recommend the use of a gastro protective agent, such as a proton pump inhibitor (PPI), with oral NSAIDs to reduce gastrointestinal adverse events (AEs). Diclofenac is a nonselective COX inhibitor type belonging to the heterocyclic arylacetic acid derivative subtype of nonsteroidal anti-inflammatory drugs. Conventionally, diclofenac sodium has been used in the treatment of OA. However, diclofenac has shown an increase in the incidence of adverse effects such as abdominal pain, dyspepsia, diarrhea, heartburn, and GI ulcer. Therefore, tramadol is now being increasingly used in OA. Tramadol is a centrally acting analgesic with the opioid-like activity of tramadol derives from low-affinity binding to μ-opioid receptors and higher affinity binding of the principal active metabolite, O-desmethyl tramadol, denoted M1, to μ-opioid receptors, and it is a commonly used opioid.[15] Tramadol has a better ability to reduce pain which is primarily responsible for limitation and disability in patients with OA. Greater reduction in pain leads to a better quality of life in patients with OA. There is a paucity of data where a comparison between these two drugs has been done in the Indian population. Hence, we conducted a study on patients of OA treated with the traditional drug diclofenac sodium and compare it with tramadol, with the primary objective for determining effectiveness and tolerability based on WOMAC scores.

METHODS

The study was conducted as a randomized clinical study of the effectiveness and tolerability of tramadol versus diclofenac in the treatment of knee OA, at Tertiary care institute of Gujarat in the department of orthopedics from January 2020 to August 2020. Ethical approval was taken from the institutional ethical committee and written informed consent was taken from all the participants.

Inclusion criteria

Male and female patients who were ≥ 39 years of age and radiological diagnosed with osteoarthritis of the knee were included in the study.

Exclusion criteria

Patients with a history or showing the presence of other rheumatic disease that would be responsible for secondary osteoarthritis, patients with a history of peptic ulcers, patient with a history of bleeding disorders, patients with renal impairment, alcoholic liver disease, pregnant or lactating woman, uncontrolled medical conditions like severe anemia, hypertension, congestive cardiac failure and bronchial asthma were excluded from the study.

Consecutive patients were allotted serially in two groups; tramadol group (n=75) One tablet orally twice daily for 8 weeks. Diclofenac group (n=75) patients received 75 mg oral dose of diclofenac 2 times daily for a period of 8 weeks. The patients are selected from an age group since this is age group commonly involved with OA.

Follow up

After 2 months of taking of treatment patients were followed up by following methods: The change in the scoring of pain domain of WOMAC OA index, the change in the scoring of stiffness domain of WOMAC OA index, the change in the scoring of difficulty in performing daily activities (DPDA) domain of WOMAC OA index, the change in WOMAC score (overall), the change in the scoring of knee joint tenderness, tolerability was assessed based on the adverse events reported.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS

Among the total n=150 patients, n=90 patients were females and n=60 were males. In the diclofenac group, there were n=46 females and n=29 males and in the tramadol group, there were n=29 females and n=31 males. The change in the scoring of stiffness domain of the WOMAC OA index questionnaire in both the study groups was measured (Table 1). About 33% decrease in the scoring of stiffness domain of the WOMAC OA index questionnaire in the tramadol group and a 21% decline in the diclofenac group was observed. The change in the scoring of DPDA domain of the WOMAC OA index in both the study groups was assessed. A 27% decrease in the scoring of DPDA domain of WOMAC OA index questionnaire scoring in the tramadol group and a 22% reduction in the diclofenac group were observed (Table 1). The change in the WOMAC score (overall) in both the study groups was analyzed. A 32% decrease in the WOMAC score (overall) in the tramadol group and a 23% decline in the diclofenac group were seen.

The change in the scoring of knee joint tenderness in both the study groups was assessed (Table 2). There was a 65% decrease in the scoring of knee joint tenderness questionnaire in the tramadol group and a 44% reduction in the diclofenac group. Tramadol was found to be more effective in improving the WOMAC OA index. WOMAC score (overall) and knee joint tenderness scores were also improved by tramadol than diclofenac. Diclofenac and tramadol groups were compared by paired t-test and unpaired t-test, they were found to be statistically significant in parameters in study groups. When the mean difference within the two study groups was compared statistically, the change in the scoring of pain domain of the WOMAC OA index was p<0.05. The mean difference within the two study groups was compared and the change in the scoring of stiffness domain of WOMAC OA index was p<0.05. The comparative analysis of the mean difference in the two study groups was statistically analyzed; the change in the scoring of DPDA domain of the WOMAC OA index was p<0.05. The mean difference within the two study groups was compared by t-test, the change in WOMAC score (overall) was p<0.05. Mean difference within the tramadol and diclofenac groups was statistically compared, the change in the scoring of knee joint tenderness was p <0.05. In the tramadol group, one patient reported epigastric discomfort, two patients complained of dyspepsia, one patient reported diarrhea, two patients complained of nausea, three patients suffered constipation, and two patients complained of flatulence. Within the diclofenac group, five had epigastric discomfort, four complained of dyspepsia, two had diarrhea, four had nauseas, two had constipation, and one complained of flatulence.

Table 1: The change in the scoring of pain domain, stiffness domain, and DPDA domain of the WOMAC osteoarthritis index and WOMAC score (overall) in both the study groups.

Variable	Tramadol group			Diclofenac group		
	1st visit	2nd visit	P value	1st visit	2nd visit	P value
Scoring of pain domain questionnaire	11.90±1.21	7.10±2.02	0.05*	11.85±1.26	8.2±1.11	0.004*
Scoring of stiffness domain questionnaire	4.03±0.3	2.40±0.6	0.001*	4.2±0.4	3.1±0.2	0.03*
Scoring of DPDA domain questionnaire	39.9±2.5	29.1±02.01	0.02*	39.1±2.7	30.01±1.22	0.001*
WOMAC score (overall)	55.9±2.4	38.8±2.12	0.01*	56.2±3.40	41.9±01.1	0.02*

*Indicates statistically significance at p≤0.05

Table 2: Change in the scoring of knee joint tenderness.

Variable	Tramadol group			Diclofenac group		
	1st visit	2nd visit	P value	1st visit	2nd visit	P value
Scoring of knee joint tenderness	1.31±0.22	0.41±0.28	0.01*	1.11±0.97	0.80±0.4	0.05*

*Indicates statistically significance at p≤0.05

DISCUSSION

Until recently the new COX-2 selective inhibitors have been increasingly used. They have equal efficacy to standard NSAIDs.[16,17] In the study, there has been a decrease in all three domains of the WOMAC OA index questionnaires scoring with both the tramadol group and the diclofenac group. In this study, there was a 15% decrease in time taken to walk 100 feet in the diclofenac group and a 17% decrease in the tramadol group. We found that there was a 41% decrease in pain score at rest in diclofenac and a 49% decrease in the tramadol group. A decrease in pain score during active movement was 32.4% in diclofenac and 44.8% decrease in the tramadol group. The results also revealed that there was a 44% decrease in joint tenderness score in diclofenac and 65% of the tramadol group which was significant. Tramadol was superior to diclofenac in decreasing joint tenderness score clinically as well as statistically. Assessment of disease status and response to therapy was made on a 0-4 Likert scale by the investigators. There was a 44% improvement in disease status in the diclofenac group and a 65% increase in the tramadol group. Assessment of response to the drug was made on a 0-4 Likert scale by the patient. Patient response to tramadol was better than diclofenac clinically as was as statistically. Pareek et al[18] compared aceclofenac with diclofenac and it was found that aceclofenac was superior to diclofenac in decreasing WOMAC score. Ward et al[19] found aceclofenac and diclofenac were equally effective in decreasing pain on weight-bearing, pain at rest, and pain during active movements on VAS. Sridhar et al comparing the efficacy of tramadol and aceclofenac in the treatment of OA found that aceclofenac was efficacious as compared to tramadol in the treatment of OA.[20] Malonne et al studying the tolerability of tramadol in the treatment of OA found that long-term treatment with tramadol once daily was generally safe in cases of OA.[21] Tramadol is an analgesic that has incredible use in acute pain, chronic pain, cancer pain, etc., mostly due to its dual mode of action.[22] In an earlier study, IR tramadol was compared with IR

diclofenac in OA patients.[23] Both medications were given as needed, to a maximum dose of 300 mg/day for tramadol and 150 mg/day for diclofenac. Correspondingly, patients experienced greater functional improvement in the overall WOMAC pain, stiffness and function scores in the present study, compared with the study.[23] But as evident from the graphs mean scores for all the parameters has substantially increased in all the treatment groups with maximum increase in DIC+PPI group reflecting its maximum efficacy compared to tramadol group. This can be because diclofenac gets distributed in synovial fluid and has chondro protective and other action as mentioned like blockage of voltage-dependent sodium channels and acid-sensing ion channels (ASICs), positive allosteric modulation of KCNQ-and BK-potassium channels.[24] And addition of PPI may be responsible for increase efficacy due to its anti-inflammatory action as well as antisecretory action which decreases gastrointestinal adverse effect and increases compliance.[25,26]

Tramadol is an analgesic that has incredible use in acute pain, chronic pain, cancer pain, etc., mostly due to its dual mode of action.[27] The effectiveness and safety of tramadol for musculoskeletal pain attributed to OA are spectacular.[28] Some of the concerns with nonsteroidal anti-inflammatory drugs (NSAIDs) are they are toxic to articular cartilage and have deleterious effects on bone healing.[29,30] Although tramadol does not have anti-inflammatory properties its central action could be of benefit as it decreases the central neuronal sensitization due to persistent nociceptive inputs.[31] The incidences of ADRs are lesser with tramadol and it was better tolerated with fewer incidences of GI adverse effects as commonly seen with NSAIDs like an observation of other studies.[32,]

CONCLUSION

Since long term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events. There was a significant improvement in the standard of life in patients suffering from knee OA when treated with tramadol. Tolerability was better with tramadol than diclofenac. Although, clinicians may be compelled in some circumstances to use diclofenac due to its anti-inflammatory properties which are required in cases of OA where inflammation is severe. Therefore, the use of clinical judgment is paramount in deciding the drugs to be used, and sometimes a combination of both can be tried under appropriate circumstances.

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