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Original Research Article

A Double Blind Randomized Controlled Trial Assessing Oxaceprol versus Tramadol for Knee Osteoarthritis

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to compare the efficacy and tolerability of oxaceprol, in comparison to the relatively weak opioid tramadol, in the treatment of symptomatic knee osteoarthritis.

Material & Methods: A parallel group, double-blind, randomized controlled trial was carried out in the Department of Pharmacology, Anugrah Narayan Magadh Medical College and Hospital Gaya, Bihar, India from October 2018 to December2019. This retrospective study was carried among patients diagnosed as Osteoarthritis. Consent was taken from the patient. A total of 200 patients were included in the study with knee joint pain intensity of at least 35 mm on a 100 mm visual analogue scale (VAS) present for at least preceding 3 months and with confirmed degenerative changes in knee skiagram.

Results: In tramadol group, 47% were males and 53% were females and mean age of participants was 52.48 years whereas in Oxaceprol group 49% were males and 51% were females and mean age of participants was 51.39 years. No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up. No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up.

Conclusion: Efficacy and tolerability of oxaceprol were comparable to tramadol, and the drug can be considered as an alternative to low-potency opioids in the management of knee osteoarthritis.

Keywords: Knee, osteoarthritis, oxaceprol, randomized clinical trial, tramadol

Introduction

Osteoarthritis (OA) is a chronic, degenerative disease of synovial joints of unknown origin which is characterized by gradual loss of articular cartilage and affects bone of both large and small joints and progressively interferes with the ability to work and depending on the joints involved, the activities of daily living. It is the most prevalent disease with a worldwide distribution. [1] OA joints include progressive loss and destruction of articular cartilage, formation of osteophytes, variable degrees of inflammation of the synovium, thickening of the subchondral bone, degeneration of ligaments and menisci and hypertrophy of the joint capsule. [2] The primary symptoms are pain and stiffness of the affected joints, secondarily leading to joint dysfunction, deformities, and muscular weakness. Previously osteoarthritis was thought to be a normal consequence of aging but now proved that osteoarthritis results from a group of multiple factors such as genetic predisposition, mechanical forces, local inflammation by cellular and biochemical processes. [3] Osteoarthritis of knee is the most common form of arthritis. Approximately 250 million people are suffering from osteoarthritis of the knee alone throughout the world. [4] According to the WHO report (2017), 18% of women and 6.9% of men aged over 60 suffer from osteoarthritis. [5] In Asia, it is estimated the fourth leading cause of disability, the prevalence of osteoarthritis in the Indian population is about 4% in urban and 6% in rural areas. [6] There are as yet no clinically proven therapies to halt osteoarthritis onset or progression. The traditional pharmacological approach is mostly limited to symptomatic management of pain using analgesics, starting with paracetamol and then moving on to nonsteroidal anti-inflammatory drugs (NSAIDs), less potent opioids like tramadol and finally to potent opioids such as oxycodone or

hydromorphone. The current treatment of OA is generally focused on symptomatic relief by use of rapid action drugs like analgesics and NSAIDs and newer cyclooxygenase (COX-2) specific inhibitors. NSAIDs intake increases the risk of gastritis and does not have direct impact on the underlying pathogenesis of articular diseases, thus have minimal role in modifying disease course and improving quality of life. COX -2 inhibitors have less incidence of gastrointestinal adverse events but may have significant renal and cardiovascular toxicities. Hence, there is continuous search of new and better drug for OA. [7] Tramadol augments serotonergic and noradrenergic neurotransmission, although it's main active metabolite, Desmethyltramadol. [8] Guidelines suggest tramadol as the first-line drug for mild to moderate pain. . [9] Also it has been observed that tramadol is modestly effective for osteoarthritis-related pain in placebo-controlled trials. [10] The search for a truly disease modifying anti‑osteoarthritis drug remains elusive. Oxaceprol (N-acetyl-L-hydroxyproline), is an atypical inhibitor of inflammation, used as a drug for joint disease without less side-effects with better safety profile than non-steroidal anti-inflammatory drugs (NSAIDs). [11] Oxaceprol has anti-inflammatory and analgesic efficacy comparable to the conventional non-steroidal anti-inflammatory drugs (NSAIDs) but has a different mode of action. Instead of inhibiting the synthesis of prostaglandins oxaceprol prevents leukocyte infiltration into the joints, thus inhibiting an early step of inflammatory cascade and presenting a novel class of anti-inflammatory agents. By this mechanism, it helps to maintain joint integrity. [12,13] We, therefore, thought it worthwhile to compare the efficacy and tolerability of oxaceprol, in comparison to the relatively weak opioid tramadol, in the treatment of symptomatic knee osteoarthritis.

Material & Methods

A parallel group, double-blind, randomized controlled trial was carried out in the Department of Pharmacology, Anugrah Narayan Magadh Medical College and Hospital Gaya, Bihar, India from October 2018 to December 2019. This retrospective study was carried among patients diagnosed as Osteoarthritis. Consent was taken from the patient. A total of 200 patients were included in the study with knee joint pain intensity of at least 35 mm on a 100 mm visual analogue scale (VAS) present for at least preceding 3 months and with confirmed degenerative changes in knee skiagram.

Patients with morning stiffness of over 30 min, secondary osteoarthritis, knee injury or diagnostic arthroscopy of signal knee within 6 months advanced osteoarthritis, deformed joint, and any serious concomitant disease were excluded from the study. Participants were randomized in two study groups of 100 patients each. Each group was given either oxaceprol 200 mg capsule or tramadol 50 mg capsule, thrice daily after food, for 12 weeks. The primary efficacy variable for this study was symptom relief and was assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain, stiffness, and physical function measured on a 100 mm visual analogue scale (VAS). Patient's Clinical Global Impression (CGI) was reported on a 5-point Likert scale as much worsened, worsened, no change, improved and much improved. Rescue medication used during the study period was also recorded. Complete blood count, blood glucose, liver function tests, and serum creatinine was recorded at the start of the study and. Vital signs were recorded at each visit and adverse events were reported.

Exclusion Criteria

Patients with morning stiffness of over 30 min, secondary osteoarthritis, knee injury or diagnostic arthroscopy of signal knee within 6 months advanced osteoarthritis, deformed joint, and any serious concomitant disease.

Participants were randomized in two study groups of 100 patients each group by computer generated random number list. Each group was given either oxaceprol 200 mg capsule or tramadol 50 mg capsule, thrice daily after food, for 12 weeks. The primary efficacy variable for this study was symptom relief stiffness, and physical function, measured on 100 mm Visual analogue scale (VAS) scale. Rescue medication used during the study period was also recorded.

Complete blood count, blood glucose, liver function tests, and serum creatinine was recorded at the start of the study and. Vital signs were recorded at each visit and adverse events were reported.

Statistical analysis

In the present study the data have subjected to Paired and Independent t-test as applicable. P values less than 0.05, 0.01 and 0.001 were considered as significant, very significant and highly significant respectively.

Results

Table 1: Demographic data

Parameters	Tramadol group (n=100)	Oxaceprol group (n=100)
Male n (%)	47 (47%)	49 (49%)
Female n (%)0.8415	53 (53%)	51 (51%)
Age years (mean ± SD)	52.48±10.5	51.39±9.71

In the present study a total of 200 patients randomized in two study groups of 100 patients each were included in the study. Each group was given either oxaceprol 200 mg capsule or tramadol 50 mg capsule. In tramadol group 47% were males and 53% were females and mean age of participants was 52.48 yrs whereas in Oxaceprol group 49% were males and 51% were females and mean age of participants was 51.39 yrs. No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up.

Table 2: Western Ontario and McMaster Universities Osteoarthritis Index score

		Baseline	After 6 monthsfollow-up	p-value
		(mean ± SD)		
WOMAC Pain	**Oxaceprol**	314.02±55.75	204.6±57.63	<0.05
	Tramadol	325.25±66.24	201.19±94.26	
WOMAC stiffness	**Oxaceprol**	34.16±10.24	22.48±8.40	
	Tramadol	32.28±9.32	24.46±6.42	
WOMAC physical function	**Oxaceprol**	1042.65±204.6	745.5±272.18	
	Tramadol	1107.43±241.39	825.55±274.3	

No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up.

Discussion

Osteoarthritis is a degenerative disease of synovial joints that affects cartilage and bone of both large and small joints and progressively interferes with the ability to work and depending on the joints involved, the activities of daily living. The primary symptoms are pain and stiffness of the affected joints, secondarily leading to joint dysfunction, deformities, and muscular weakness. It is the most common form of arthritis with approximately 250 million people worldwide conservatively estimated to be suffering from osteoarthritis of the knee alone. [14] Previously thought to be a normal consequence of aging, it is now realized that osteoarthritis results from a complex interplay of multiple other factors such as genetic predisposition, mechanical forces, local inflammation, and cellular and biochemical processes. [15] The current treatment of OA is generally focused on symptomatic relief by use of rapid action drugs like analgesics and NSAIDs and newer cyclooxygenase (COX-2) specific inhibitors. NSAIDs intake increases the risk of gastritis and does not have direct impact on the underlying pathogenesis of articular diseases, thus have minimal role in modifying disease course and improving quality of life. COX -2 inhibitors have less incidence of gastrointestinal adverse events but may have significant renal and cardiovascular toxicities.

In tramadol group, 47% were males and 53% were females and mean age of participants was 52.48 years whereas in Oxaceprol group 49% were males and 51% were females and mean age of participants was 51.39 years. No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up. Bauer et al. compared oxaceprol (200 mg thrice daily) with diclofenac (25 mg thrice daily) over 3 weeks in a multicentre, randomized, double-blind, study in Germany. Joint function, evaluated by Lequesne's indices, improved clinically in both treatment arms. In both groups VAS score for pain was reduced nearly 50%, joint mobility improved nearly 60% and pain-free walking period more than doubled. Differences between groups were not significant. The incidence of ADRs was similar in both groups but oxaceprol induced milder symptoms. [16]

No statistically significant difference was observed between groups for WOMAC scores. Significant reduction in pain, stiffness and physical function was observed between oxaceprol and tramadol group at baseline and after 6 months follow-up. The study published by Herrmann et al. also showed the equivalence of oxaceprol with diclofenac in a comparable study design but with higher dosage (diclofenac 3 x 50 mg/day orally and oxaceprol 3 x 400 mg / day orally). The Lequesne index improved by 2.5 points in the oxaceprol and by 2.8 points in the diclofenac group. The weight-bearing pain also improved clearly (oxaceprol –2.2 of 10 points, diclofenac –2.3 of 10 points). [17] Swathi C et al compared the effectiveness and tolerability of tramadol versus diclofenac in treating chronic pain due to knee OA. There was a 16.73% decrease in time taken to walk 100 feet in the diclofenac group and an 18.30% decrease in the tramadol group. There was a 42.85% decrease in pain score at rest in diclofenac and a 50.72% 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. [18]

Conclusion

The present study concluded that Oxaceprol efficacy and tolerability was comparable with tramadol and the drug can be considered as an alternative to low-potency opioids in the management of knee osteoarthritis.

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