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ORIGINAL ARTICLE

Comparison of NSAIDS Versus NSAIDS Plus Duloxetine in Knee Osteoarthritis Patients

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ABSTRACT

Objective: To compare the efficacy of Duloxetine with NSAIDS versus NSAIDS alone for the treatment of knee pain secondary to osteoarthritis.

Study Design: Randomized clinical trial study.

Setting and Duration: Department of Rheumatology, PIMS Hospital, Islamabad, from April to August 2021.

Methodology: One hundred and twenty eight patients with knee osteoarthritis were included in the study and were divided in two equal groups; one group was subjected to Duloxetine plus NSAIDs and other to just NSAIDs. The response was assessed at end of 3 months. Reduction in pain more than or equal to 50% from the baseline was considered as efficacy.

Results: The mean VAS score was 3.56±1.15 in group A (Duloexetine plus NSAIDS) A while in group B (NSAID alone), 4.45±1.22 and significantly (p-value > 0.05). Similarly, the comparison of WOMAC score for pain showed that the mean WOMAC score was significantly (P-value > 0.05) less 5.68±1.56 in group A in contrast to 6.39 ± 1.69 in group B. Comparison of efficacy between two groups showed that the rate of efficacy was significantly (P-value >0.05) higher in group A 48.4% as compared to 31.3% in group B.

Conclusion: Addition of Duloxetine to NSAIDs resulted in more reduction of pain in terms of VAS and WOMAC score with acceptable adverse effects.

Keywords: Chronic pain**,** Duloxetine, Knee pain, NSAIDs, Osteoarthritis

INTRODUCTION

The most prevalent form of arthritis in elderly people is osteoarthritis of the knee (OAK), which is one of the most common chronic diseases globally. Osteoarthritis develops as a result of the destruction of protective cartilage at the ends of bones over time. This condition usually worsens with time, making the quality of life poorer and increasing depression and anxiety levels of the patients. It has a quite high prevalence of 44.7% in the general population, but the risk of its incidence further increases in older age, female population, and in obese persons.[1] Generally, Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are considered in the treatment of joint soreness and improving quality of life and lower limb function of the patients with OA. The most commonly prescribed oral NSAIDs are diclofenac, ibuprofen, and naproxen for the treatment of osteoarthritis.

Oral NSAIDs' effectiveness, safety, and tolerability have been widely researched, including studies from the Agency for Healthcare Research and Quality and the American College of Rheumatology (ACR).[2,3]

While the major drawbacks are safety and tolerability, effectiveness can also be an issue; in fact, only a limited percentage of patients who use NSAIDs for OA pain achieve a patient-acceptable symptom state. In a 2007 meta-analysis of 23 randomized, placebo-controlled studies involving 10,845 patients, the NSAID treatment group demonstrated a 15.6 percent better improvement in pain than the placebo group after 2 to 13 weeks of medication.[4] The alternate therapies for the management of OA, are intra-articular injections of steroids or hyaluronic acid and oral opioids in patients in which NSAIDs fail to give considerable pain relief. Duloxetine (a dual reuptake inhibitor), norepinephrine, and serotonin have been proved to give very good results in relieving pain associated with osteoarthritis of the knee.

Chronic pain is a disease characterized by structural and functional abnormalities in the peripheral and central nervous systems. Central sensitization and impairment of related pain inhibitory circuits have been widely studied among these abnormalities. The common underlying etiologies of OA may include inflammation, neuropathy, and tissue damage etc. These pathophysiological processes are largely the responsible or associated factor for the development and maintenance of chronic pain states in OA.[5]

In chronic pain, the net inhibitory effect of these monoamines is considered to be reduced or lost, causing the descending pain modulatory system to switch from an inhibitory to a positive and constructive state. Duloxetine is a potent and specific inhibitor of 5-HT and NE reuptake in the central nervous system (CNS) in vitro and in vivo. According to preclinical research, duloxetine significantly reduces pain behavior in a variety of chronic, neuropathic, and inflammatory pain models at a dosage range consistent with inhibition of 5-HT and NE reuptake. Duloxetine's analgesic impact is thought to be due to enhanced 5-HT and NE activity in the CNS, probably through increasing descending pain inhibitory pathways in the brain and spinal cord or other undiscovered CNS activities.[6,7]

In previously published trials of duloxetine for OA pain, patients were categorized based on their self-reported oral NSAID and acetaminophen use at study entry. In one of the experiments, the duloxetine group (65.35) had a considerably higher BPI average pain response rate[8] (30% pain reduction from baseline to endpoint) than the placebo group (44.1%, P=0.001). However, based on 50%

response rate of BPI, there was no significant difference in average pain between the treatment groups (duloxetine, 43.8% vs. placebo, 32.3%; P = 0.068).[9]

Duloxetine is beneficial in the treatment of people with chronic pain in previous clinical trials. Duloxetine's effectiveness in OA pain has also been documented in placebo-controlled trials. In our population, the amount of data available is very limited. So, the present study has been designed to find the efficacy of duloxetine along with NSAID in comparison to NSAID alone in our population in patients with knee pain secondary to osteoarthritis.

MATERIALS AND METHODS

This randomized clinical trial study was conducted in the Department of Rheumatology, Pakistan Institute of Medical Sciences Islamabad. A total of 128 patients were enrolled, which were divided into two equal groups of 64 patients in each group (group A and group B). In group A Duloxetine was added to oral NSAIDs which the patient was already taking. Group B was given NSAIDs usual treatment of the patient. Patients of both genders having an age range from 40 to 80 years old, with OA of the knee joints for 3 or more months of a grade less or equal to 3 on Kellgren Lawrence grading were selected for the study. The patients with pain of moderate to severe intensity (Visual Analog Scale score of 4 or more) and WOMAC score of 8 or more out of 20 using NSAIDs for three or more months and given one week of washout phase was included. Patients having a history of gout, pseudogout or inflammatory arthritis, end-stage, bone-on-bone OA, have gone through any kind of knee surgery, steroid or PRP intra-articular injection in the last 6 months, with the diagnosis of fibromyalgia, BMI >40 kg/m^2, history of peptic ulcer disease or contraindication for Duloxetine were excluded. Demographics including age, gender, body mass index (BMI), and duration of knee pain were recorded for all the patients. The dose of the oral NSAIDs was optimized at the discretion of the physician before the start of the trial. PPIs were continued if patients already taking or added if not taking as 20 mg/day before breakfast. The baseline knee pain was measured through VAS (0-10) and WOMAC score for pain (0-20). The dose of the Duloxetine was 30 mg/day at the start of the trial. Patients were followed at the end of 4 weeks, then the dose of duloxetine was increased to 60 mg/day. Patients were finally evaluated at the end of 3 months and reduction in pain was assessed. Reduction in pain more than or equal to 50% from the baseline was considered as efficacy while this information was noted.

Data entry and statistical analysis was carried out using the SPSS-25. An Independent sample t-test was applied to compare VAS and WOMAC scores and differences in these scores after treatment between both groups. The efficacy of both groups was compared between both groups by applying the Chi-square test. P-value <0.05 was considered significant.

RESULTS

The mean age of the patients in group A was 48.94±5.8 years and in group B was 49.17±5.22 years. Females were in majority in both groups (75% vs. 65.6%) without any significant (P>0.05) difference between both groups. The majority of the patients in both groups (46.87% vs 54.68%) were obese (BMI> 30) without any statistically significant (P-value >0.05) difference. The duration of osteoarthritis was similar in both groups (P-value > 0.05) with a mean value of 1.67±0.92 years in group A and 1.44±0.73 years in group B (Table 1).

The baseline mean VAS score in group A was 7.13±1.54 and it reduced to 3.56±1.15 after treatment. The mean WOMAC score at baseline was noted to be 10.92±2.27, which reduced significantly (P-value <0.05) to 5.68±1.56 after three months of treatment in group A. In patients of group B who were treated with NSAID alone, it was observed that the mean VAS score reduced significantly (P-value <0.05) from 7.58±1.63 to 4.45±1.22 and mean WOMAC score from 11.61±2.17 to 6.39±1.69 after three months treatment (Table 2).

The comparison of efficacy (more than 50% reduction in pain score) between both groups showed that the rate of efficacy was significantly (P-value >0.05) higher in combination group A (48.4%) as compared to (31.3%) group B in which NSAID alone was used (table 3).

Table-1: Demographic characteristics of both groups

Characteristics	Group A	Group B	P value
Age (years)	48.94±5.8	49.17±5.22	0.835
Gender			
Male	16	22	0.246
Female	48	42	
Body Mass Index (kg/m^2)			
< 25	6	5	0.676
25-30	28	24	
> 30	30	35	
Duration of OA (yrs)	1.67±0.92	1.44±0.73	0.116

Table-2: Comparison of VAS and WOMAC scores within both groups

Characteristics	Group A	Group B	P value
VAS Score at Baseline	7.13±1.54	7.58±1.63	0.000
VAS Score at 3 months	3.56±1.15	4.45±1.22	0.000
WOMAC Score at baseline	10.92±2.27	11.61±2.17	0.000
WOMAC Score at 3 months	5.68±1.56	6.39±1.69	0.000

Table 3: Comparison of Efficacy between both drug groups

Efficacy	Group A	Group B	P value
Yes (> 50%)	31 (48.4%)	20 (31.3%)	0.047
No (< 50%)	33 (51.6%)	44 (68.8%)	

DISCUSSION

Pain is the most common complaint among patients with osteoarthritis of the knee, and it compels these patients to seek medical treatment in the majority of cases. As a result, pain reduction and functional improvement are the key factors to be controlled by clinical management.[10,11] Current recommendations propose a combination of nonpharmacological and pharmacological treatments to manage pain. Losing weight, aerobic, and/or muscle-building activities are some of the nonpharmacological remedies for OAK. Acetaminophen is suggested as the first-line therapy, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids as the second and third lines of treatment.[12] The long-term use of these drugs has safety and efficacy concerns linked with the treatment due to risks of side effects. These potential side effects may includes

nephrotoxicity, gastrointestinal bleeding, peptic ulcer disease, serious long-term cardiovascular effects of NSAIDs, respiratory depression, overdose and dependency (opioids).[13]

The results of this present study showed that the mean age of the patients in both groups was higher (48.94±5.8 vs 49.17±5.22 years) and females were in majority in both groups (75% vs. 65.6%). The majority of the patients in both groups (46.87% vs. 54.68%) were obese (BMI >30).The majority of previous research supports the conclusions that this condition is more frequent in older people, women, and obese people.[14]

As first and second lines of therapy, NSAIDs and opioids are suggested. However, concerns about the long-term safety and effectiveness of NSAIDs and opioids have been expressed. Some reviews have gone even farther, warning against long-term usage. According to recent meta-analyses, currently available oral therapies are only moderately effective in the average OA patient. Furthermore, trial efficacy appears to be influenced by trial design and baseline characteristics and may be constrained to the first few weeks of treatment.[15,16]

Duloxetine, a selective serotonin-norepinephrine reuptake inhibitor, has been shown to be beneficial in the treatment of knee OA in several randomised, placebo-controlled studies with an acceptable safety profile. The use of duloxetine is recommended in all individuals with or without comorbid conditions along with multiple-joint OA. These recommendations are based on treatment guidelines of Osteoarthritis Research Society Internation (OARSI). These recommendations are valid with uncertain suitability among the patients of knee-only OA having comorbidities.[17]

The results of this present study also showed that the duloxetine group had higher efficacy as compared to the standard treatment group who received NSAIDs alone. The finding from this study showed that the mean VAS score in (duloxetine + NSAID) group (3.56±1.15 vs. 4.45±1.22) was significantly (p>0.05) less as compared to (NSAID alone) group. Similarly, the comparison of WOMAC score showed that the mean WOMAC score was significantly (P>0.05) less (5.68±1.56) in group A in contrast to (6.39±1.69) in group B. These findings are consistent with many other studies that have seen significant improvements in VAS and WOMAC scores. Duloxetine treatment significantly improved all of the individual women items in this sample group when compared to placebo, demonstrating that pain reduction from duloxetine administration was linked to improvements in OA-specific HRQoL components in patients with knee osteoarthritis.[18,19]

It was found in this study that the comparison of efficacy (more than 50% reduction in pain score) between both groups showed that the rate of efficacy was significantly (P>0.05) higher in combination group A (48.4%) as compared to (31.3%) group B in which NSAID alone was used. These results are in very much agreement with previous studies that showed that in terms of pain intensity reduction, the patients treated with duloxetine had statistically significant better results as compared to patients treated with NSAIDs alone. The response rate of (30% and 50%) was noted to be significantly higher in duloxetine group as compared to control group. Higher proportions of patients were noted in duloxetine group, experiencing moderate to substantial improvement.[20]

Physical functioning improved more in duloxetine patients than in those receiving conventional therapy (e.g. walking, rising from sitting, bending, climbing stairs). Patients treated with additional duloxetine reported a higher sense of overall improvement than those treated with an NSAID alone. Furthermore, the worst pain, overnight pain, and pain during the five activities assessed by the WOMAC pain scale (walking, climbing stairs, in bed, sitting or lying, and standing) all improved significantly.[10]

The safety profile of duloxetine in this trial resembled that of earlier duloxetine studies for the treatment of OA and other conditions. This information should help clinicians evaluate the benefits and drawbacks of adding duloxetine to their patients' therapeutic interventions.[21]

Limited number of study with use of duloxetine in use of knee OA present in local population providing gateway to future studies for use of duloxetine in damaged tissues in suppressing the neuropathic pathway and its role in OA of other joints could be established. Limited number of patients has access to knee replacements procedures and not everyone is eligible as surgical candidate could benefit from duloxetine.

CONCLUSION

Treating knee osteoarthritis with duloxetine in addition to NSAIDs results in a higher reduction in pain, some functional improvement with acceptable adverse effects when compared to NSAIDs alone were found. Patients with persistent and refractory pain from knee osteoarthritis should consider duloxetine, which can be utilized in combination with NSAIDs to provide long-term relief.

REFERENCES

1. Wang ZY, Shi SY, Li SJ, Chen F, Chen H, Lin HZ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain Med 2015;16(7):1373-85.
2. McDonagh MS, Selph SS, Buckley DI, Holmes RS, Mauer K, Ramirez S, et al. Nonopioid pharmacologic treatments for chronic pain. comparative effectiveness review No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality; April 2020.
3. American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Anti-inflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American College of Rheumatology white paper. Arthritis Rheum 2008;59(8):1058-73.
4. Bjordal JM. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11:125-38.
5. Skljarevski V, Zhang S, Iyengar S, D'Souza D, Alaka K, Chappell A, Wernicke J. Efficacy of Duloxetine in Patients with Chronic Pain Conditions. Current Drug Therapy 2011; 6:296-303.
6. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. ProgNeurobiol 2009; 87: 81-97.
7. Bellingham GA, Peng PW. Duloxetine: a review of its pharmacology and use in chronic pain management. Reg Anesth Pain Med 2010;35:294-303.

8. Brown JP, Boulay LJ. Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee. Ther Adv Musculoskelet Dis 2013:291-304.
9. Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11(1):33-41.
10. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27(12):2361-72.
11. Kirazli Y. Current approach to the guidelines for the diagnosis and treatment of osteoarthritis. Turk J Geriatr-Turk Geriatr Dergisi 2011;14:119-25.
12. Conaghan PG, Dickson J, Grant RL. Guidelines: care and management of osteoarthritis in adults: Summary of NICE guidance. Br Med J 2008;336:502.
13. Drini M. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. Aust Prescr 2017;40(3):91-3.
14. Muraki S, Oka H, Akune T. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17(9):1137-43.
15. Myers J, Wielage RC, Han B, Price K, Gahn J, Paget MA, et al. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. BMC Musculoskeletal Disordr 2014;15:76.
16. Afzal M, Khan A, Rizvi F, Hussain A. Patients satisfaction levels in outpatient department of a teaching hospital. J Islamabad Med Dent Coll 1012;11(1):26-9.
17. Wang G, Bi L, Li X. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2017;25(6):832-38.
18. van Dijk GM, Veenhof C, Schellevis F. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95.
19. Enomoto H, Fujikoshi S, Ogawa K, Tsuji T, Tanaka S. Relationship Between Pain Reduction and Improvement in Health-Related Quality of Life in Patients with Knee Pain Due to Osteoarthritis Receiving Duloxetine: Exploratory Post Hoc Analysis of a Japanese Phase 3 Randomized Study. J Pain Res 2020;13:181-91.
20. Brown JP, Boulay LJ. Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee. Ther Adv Musculoskelet Dis 2013;5:291-304.
21. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis. Korean J Intern Med 2019;34(5):966-73.