A Comparative Study on Management of Pain in Patients with Osteoarthritis Receiving Monotherapy of Piroxicam Verses Piroxicam in Combination with Duloxetine

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Abstract: *Osteoarthritis is the most common bone disorder accounting for the majority of long - term disabilities as it usually affects weight - bearing joints such as the cervical, lumbosacral spine, knees, hips, as well as feet. A six - month observational study was conducted in orthopedic outpatient department. Demographic data and other pertinent information were collected. The data was assessed using WOMACS and NPR scale. Group 1 received piroxicam, and group 2 received piroxicam and duloxetine. The mean of patients in Group 1 was (55.16±11.20) and in Group 2 was (58.22±10.62). In comparison of both groups Males (62%) were dominant in group 1 whereas in Group 2 females were dominant (56). The mean height of patients in Group 1 was 5.5±2.00 and in Group 2 was 5.3±1.90. The mean weight of patients in Group 1 was 67.75±11.02 and in Group 2 was 64.2±11.84. Data were assessed using an unpaired t - test. The WOMAC score, NRS rating, and CRP levels of Group B were significantly lower than Group A. When monotherapy with piroxicam fails combination therapy can be used instead of switching to opioids.*

Keywords: Comparative, OA, Pain, Piroxicam, Duloxetine

1. Background

Osteoarthritis is the most common bone disorder accounting for the majority of long - term disabilities as it usually affects weight - bearing joints such as the cervical, lumbosacral spine, knees, hips, as well as feet. (2) Osteoarthritis affects not only the entire joint but also the synovium, subchondral bone, and articular cartilage. Frequently affected joints include the carpometacarpal (CMC), proximal interphalangeal (PIP), and distal interphalangeal (DIP). Invasive procedures like an arthroscopic meniscectomy can hasten the onset of osteoarthritis in the knee joint. [11]

Primary osteoarthritis frequently affects older people and is associated with aging. Primary osteoarthritis is an idiopathic condition that develops in joints that were once healthy without a known cause. People as young as 30 years old can develop secondary osteoarthritis. [12 - 19].

The most frequent symptom of osteoarthritis is pain. which restricts the physical activity and decreases work performance. [20]. A treatment strategy can be created once the source of the pain is found. [21] Patients with OA most frequently seek medical attention for pain. [22] The current approaches to treating OA focus on educating the patient about the condition, reducing pain, enhancing and maintaining joint function, and halting or preventing the development of harmful structural changes that have an impact on the joint tissues. [23] Nonsteroidal anti - inflammatory drugs (NSAIDs) are pharmacological agents that are frequently used to treat pain. [24] The majority of

OA patients take their medications for an extended period of time, and many of them have comorbid conditions that necessitate concurrent medication, which raises the risk of side effects like GI injury. [25] More efficient and secure OA treatments are increasingly in demand. Piroxicam is an NSAID, an oxicam derivative, which are enolic acids that inhibit cyclooxygenase (COX) enzyme non - selectively. It results in inhibition of prostaglandin production, which is the main mediator of pain. It has a long half - life (t½) of approximately 50 h and available as oral formulation, and hence, it is suitable for use in OA. [26] It is also used in the management of postoperative pain, musculoskeletal disorders, and dysmenorrhea. [27] It has shown clinical efficacy in relieving pain associated with OA and rheumatoid arthritis, especially where there is an associated inflammatory component. [8]

The pain associated with osteoarthritis has been found to be reduced by duloxetine, a selective serotonin - norepinephrine reuptake inhibitor.

2. Literature Survey

Literature 1: Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta - Analysis of Randomized Controlled Trials

Authors: Wang ZY, Shi SY, Li SJ, et al. Journal of pain medicine.
"This analysis suggests duloxetine (60/120 mg QD), compared with placebo control, resulted in a greater reduction in pain, improved function and patient - rated

impression of improvement, and acceptable adverse effects for the treatment of OAK pain after approximately 10–13 weeks of treatment”.

Literature 2: The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis

Authors: Sofat N, Harrison A, Russell MD, et al. Journal of pain research.
“Pregabalin and duloxetine had efficacy in hand OA pain in our clinical study, with pregabalin showing greater effect than duloxetine for validated pain endpoints” “In our study, one or more of the following analgesics had been used by more than half of the participants prior to enrollment in the study: acetaminophen, NSAID, or codeinebased analgesics”

“When such analgesics had not previously been effective, our trial showed that pregabalin, and to a less significant degree duloxetine, may provide a realistic alternative to pain management in OA”

“In future, clinical trials that examine the efficacy of centrally acting analgesics over a longer treatment period of >12 weeks in chronic arthritic pain should be conducted” “Further studies measuring peripheral and central sensitization will be crucial to understand how pain, loss of function, comorbid conditions, and medication use contribute to the development of arthritic pain”

“Centrally acting analgesics improve pain outcomes in people with hand arthritis, offering new treatment paradigms for OA pain”.

Literature 3: The short - term effect and safety of duloxetine in osteoarthritis: A systematic review and meta analysis

Authors: Gao SH, Huo JB, Pan QM, et al. *Medicine*.
“Duloxetine was an effective and safe choice to improve pain and functional outcome in OA patients”

“The administration of 60/120 mg duloxetine significantly reduced pain in OA patients, improves physical function and alleviate stiffness of the joints”

“Despite of higher rates of TEAEs and discontinuation, duloxetine did not increase the rate of SAEs”

“This meta - analysis suggests duloxetine might be another effective and safe medication to manage OA pain”

“However, further studies are still needed to find out the optimal dosage and examine its long - term efficacy and safety on OA patients” [109].

Literature 4: Osteoarthritis Research Society International. Efficacy and safety of duloxetine in osteoarthritis or chronic low back pain: a Systematic review and meta - analysis

Authors: Weng C, Xu J, Wang Q, Lu W, Liu Z.
“Duloxetine had modest to moderate effects on pain relief, function improvement, mood regulation and improvement in quality of life with mild AEs in the treatment of OA or CLBP”

“Future RCTs should focus on comparing duloxetine with other oral drugs and assessing the long - term safety of duloxetine”.

Literature 5: Duloxetine in OsteoArthritis (DOA) study: effects of duloxetine on pain and function in end - stage hip and knee OA – a pragmatic enriched randomized controlled trial

Authors: T. Blikman, corresponding author1, 2 W. Rienstra, 1, 2 T. M. van Raaij, 3 A. J. ten Hagen, 4 B. Dijkstra, 5 W. P. Zijlstra, 5 S. K. Bulstra, 1 M. Stevens, 1 and I. van den Akker - Scheek1
Adding duloxetine treatment seems to be beneficial for end - stage knee OA patients with neuropathic - like symptoms (at risk of CS). End stage Hip OA patients seem to be nonresponsive to duloxetine.

Literature 6: Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo - controlled trials

Authors: Joseph L Micca, Dustin Ruff, JonnaAhl& Madelaine M Wohlreich
Duloxetine 60 mg was efficacious for managing OA knee pain in both age groups, but increasing the dose to 120 mg in non - responding patients did not provide additional benefit. There was no consistent signal indicating that the safety of duloxetine might differ significantly between older and younger patients.

Literature 7: Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis

Authors: Afsaneh Enteshari - Moghaddam, Ahad Azami, Khatereh Isazadehfar, Hamed Mohebbi, Afshin Habibzadeh & Parinaz Jahanpanah
Both gabapentin and duloxetine have similar and acceptable effects in pain reduction and improvement of functional status in patients with knee OA at the end of the third month's treatment. Duloxetine effects begin from the first weeks, while gabapentin effects begin gradually with the best at the end of the third month.

Literature 8: Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open - label, long - term, Phase III extension study

Authors: Uchio Y, Enomoto H, Ishida M, Tsuji T, Ochiai T, Konno S
In Japanese patients with chronic knee pain due to osteoarthritis, long - term treatment with duloxetine was well tolerated and associated with sustained improvements in pain and health - related quality of life without radiographic deterioration.

Literature 9: Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta - analysis

Authors: Mikala C. Osani and Raveendhara R. Bannuru
The results of our study indicate that duloxetine may be an effective treatment option for individuals with OA, but that use of the drug is associated with a significantly higher risk of adverse events. Patient preferences, cost considerations, and clinicians' judgment must be taken into account before the initiation of a duloxetine regimen. Future RCTs should be conducted in patients who have concomitant OA and depression to assess the specific benefits of duloxetine in these populations, and to address the real - world scenario in which duloxetine may be a more favorable option. Studies focused on the safety of long - term use of the drug should also be conducted, to assess its eligibility as an alternative to conventional treatments that are associated with a risk of SAEs with long - term use.

3. Methodology/ Approach

An observational comparative study with 100 patients was conducted in orthopaedics department. patients above 40years diagnosis with osteoarthritis of both genders were included in the study. subjects were excluded in the study based on the following in the criteria: 1) patients Below 40 years 2) Patients with COPD, renal dysfunction, comorbid psychiatric diseases, and those with history of GI bleeding. On presentation patient demographics and other pertinent information was collected. pre treatment pain is evaluated using WOMAC scale and NPR scale and the level of inflammation is detected using biomarker C - Reactive protein. Group 1 received piroxicam at the dose of 20mg where as the patients in group 2 received piroxicam and duloxetine at the dose of 20mg and 30mg respectively. A treatment period of 14 days is allotted to each group. After this post treatment analysis is done using the scale. for each patient pre and post treatment scores are compared and converted to percentage.

Study Outcomes
Our study outcomes were Better Efficacy of Duloxetine when given as an adjuvant (WOMACS) (Pain Rating Scale) and significant reduction in Biomarker (CRP).

Statistical Analysis
"Statistical Package for Social Service (SPSS) " Ver.26 was used to analyze the data. "Means and standard deviations (SD) were computed for continuous variables, while frequencies and percentages were computed for categorical variables". "Additionally, the Mann Whitney U test and the unpaired t test were also performed for the comparison of groups".

4. Results & Discussion

The inclusion criteria led to the inclusion of 100 patients in our study. The patients were assigned to Group 1 [PIROXICAM (nonselective Cox 2 inhibitor)] and Group 2 [PIROXICAM + DULOXETINE] accordingly. The average no. of patients in Group 1 were (55.16±11.20) and Group 2 were (58.22±10.62). On comparison of both groups; In Group 1, Males (62%) were dominant than females (38%)

whereas in Group 2 Females were dominant (56%) than Males (44%). Group 1 patients' average height was 5.5±2.00 and Group 2 was 5.3±1.90. Group 1 patients' average weight was 67.75±11.02 and Group 2 was 64.2±11.84. The WOMACS mean of the patients before treatment in Group 1 was 54.52±10.10 and Group 2 was 56.36±5.54 whereas after treatment in Group 1 was 39.91±6.96 and Group 2 was 23.22±6.58. "P value is <0.05 which is statistically significant". The NMRS mean of the patients before treatment in Group 1 was 8.32±1.10and Group 2 was 8.84±1.54whereas after treatment in Group 1 was 4.85±1.20 and Group 2 was 2.75±1.35. "P value is <0.05 which is statistically significant". The CRP mean of the patients before treatment in Group 1 was 82.24±31.10 and Group 2 was 74.94±35.54 whereas after treatment in Group 1 was 61.22±22.96 and Group 2 was 23.75±11.35. "P value is <0.05 which is statistically significant".

Statistical Comparison of Mean Age in the Allotted Groups:

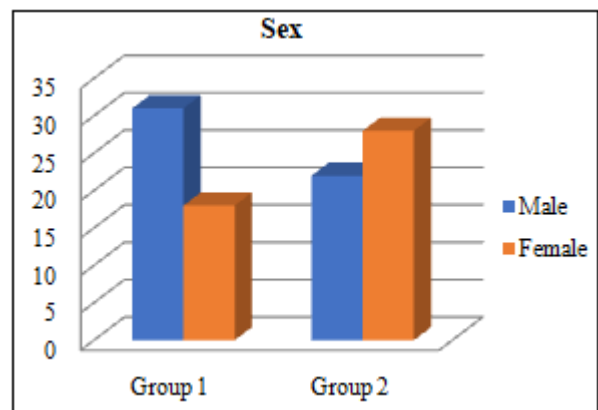| Age (Mean	Group 1	Group 2
	55.16±11.20	58.22±10.62
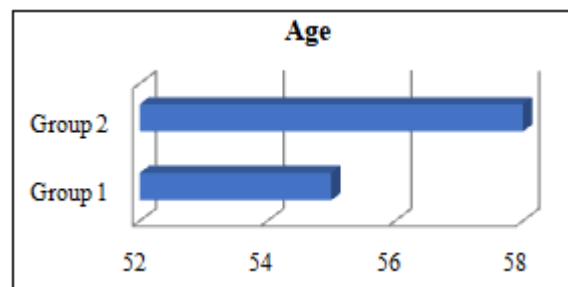
On comparison of both groups;

The mean of patients in Group 1 was (55.16±11.20) and Group 2 was (58.22±10.62).

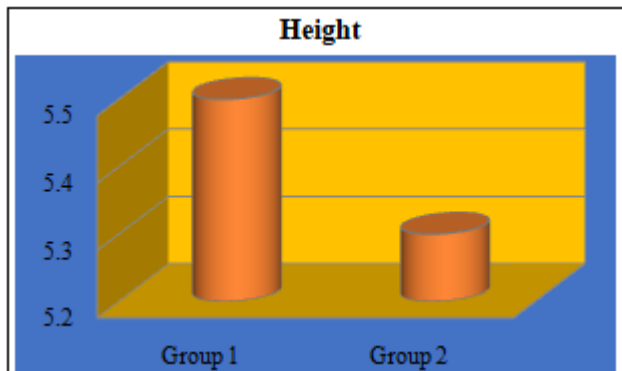**Statistical Comparison of Sex in the Allotted Groups:**

Variables	Group 1	Group 2
Male	31 (62%)	22 (44%)
Female	18 (38%)	28 (56%)

In Group 1, Males (62%) were dominant than females (38%) whereas in Group 2 Females were dominant (56%) than Males (44%).

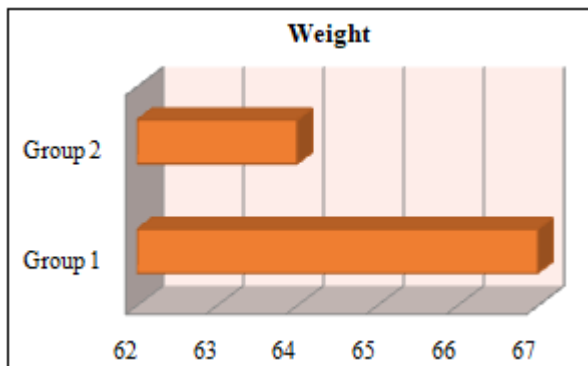**Statistical Comparison of Mean Height in the Allotted Groups:**

Height (Mean)	Group 1	Group 2
	5.5±2.00	5.3±1.90

The mean height of patients in Group 1 was 5.5±2.00 and Group 2 was 5.3±1.90.

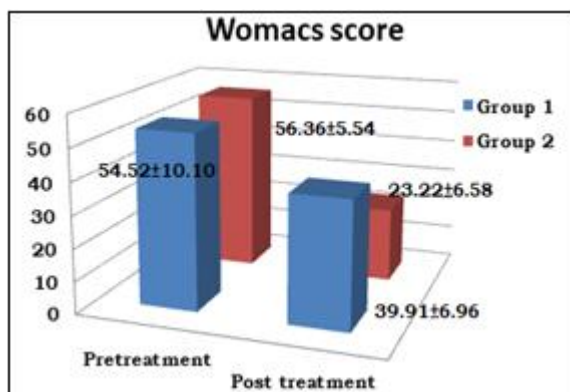**Statistical Comparison of Mean Weight in the Allotted Groups:**

Weight (Mean)	Group 1	Group 2
	67.75±11.02	64.2±11.84

The mean weight of patients in Group 1 was 67.75±11.02 and Group 2 was 64.2±11.84.

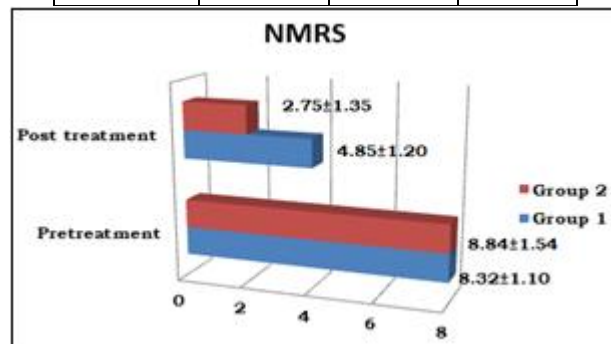**Statistical Comparison of WOMACS Score in the Allotted Groups:**

Variables	Group 1	Group 2	p value
MEAN	31.9165	23.2204	0.0001 P<0.05
SD	6.6128	5.6469	
SEM	0.9447	0.7986	
N	49	50	

There is a significant improvement in WOMACS post treatment score in group 2 than in group 1
P value < 0.05 is statistically significant

Statistical Comparison of NMRS Score in the Allotted Groups:

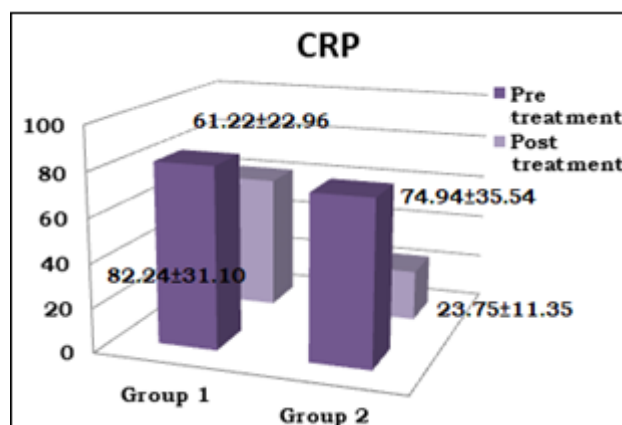| Variables	Group 1	Group 2	p value
MEAN	4.86	2.74	0.0001 P<0.05
SD	1.26	1.26	
SEM	0.18	0.18	
N	49	50	

There is a significant improvement in NPRS post treatment score in group 2 than in group 1

P value < 0.05 is statistically significant

Statistical Comparison of CRP Levels in the Allotted Groups:

Variables	Group 1	Group 2	p value
MEAN	31.22	23.30	0.0001 P<0.05
SD	8.29	9.92	
SEM	1.18	1.40	
N	49	50	

There is a significant improvement in CRP Levels post treatment score in group 2 than in group 1
P value < 0.05 is statistically significant

5. Discussion

The WOMACS score of group B was better than score reported by C. weng et al [20] and a systematic review and metaanalysis published by Shinhuagao et al [18].

GroupB's WOMACS score could not be compared as slighty different scale was used but NRS score was much better when compared with the study results reported by Nidhi sofaat et al [17]

The CRP levels were reported by neither of the conducted studies.

In our study 126 patients were enrolled in the study based on the inclusion criteria, the patients were assigned to Group 1 [PIROXICAM (nonselective Cox 2 inhibitor)] and Group 2 [PIROXICAM + DULOXETINE] accordingly. The mean of patients in Group 1 was (55.16±11.20) and Group 2 was (58.22±10.62). On comparison of both groups; In Group 1, Males (62%) were dominant than females (38%) whereas in Group 2 Females were dominant (56%) than Males (44%). The mean height of patients in Group 1 was 5.5±2.00 and Group 2 was 5.3±1.90. The mean weight of patients in Group 1 was 67.75±11.02 and Group 2 was 64.2±11.84. The WOMACS mean of the patients before treatment in Group 1 was 54.52±10.10 and Group 2 was 56.36±5.54 whereas after treatment in Group 1 was 39.91±6.96 and Group 2 was 23.22±6.58. "p value less than 0.05 or 0.05 is statistically significant". The NMRS mean of the patients before treatment in Group 1 was 8.32±1.10and Group 2 was 8.84±1.54whereas after treatment in Group 1 was 4.85±1.20 and Group 2 was 2.75±1.35. "p value less than 0.05 or 0.05 is statistically significant". The CRP mean of the patients before treatment in Group 1 was 82.24±31.10 and Group 2 was 74.94±35.54 whereas after treatment in Group 1 was 61.22±22.96 and Group 2 23.75±11.35. "p value less than 0.05 or 0.05 is statistically significant".

6. Conclusion

The WOMAC score, NRS rating, and CRP levels of GROUP B were significantly lower than Group A. When monotherapy with piroxicam fails combination therapy can be used instead of switching to opioids.

7. Future Scope

Possible ADRs can be detected and reported in patients receiving piroxicam in combination with duloxetine

8. Limitations

Shorter duration of study, ADRs not reported, Poor follow up of patients, Single site study, Duloxetine can't be administered for longer duration, Dose needs to be tapered as therapy continues, Patients with significant comorbidities are excluded.

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