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A Randomized Placebo Controlled Study to Determine the Efficacy of Oral Diclofenac Sodium in the Treatment of Symptomatic Osteoarthritis of the Knee in Nnewi, South Eastern Nigeria

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Authors' contributions

This work was carried out in collaboration between all the authors. Authors CCI and EYI designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AVE and JOU performed the statistical analysis and managed the literature searches. All the authors were involved in data collection and interpretation of data. All authors read and approved the final manuscript.

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ABSTRACT

Background: Diclofenac sodium is a non-selective non-steroidal anti-inflammatory drug (NSAID) that is widely used therapeutically for its analgesic and anti-inflammatory properties in the treatment of knee osteoarthritis (KOA) but no scientific study has been carried out at Nnewi, a town located in the Southeastern part of Nigeria to determine its therapeutic efficacy. The purpose of this study was to determine the efficacy of oral diclofenac sodium in the treatment of KOA in the local population using knee joint pain intensity, quadriceps muscle strength and 30.4 metres walk-time

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as outcome measures.
Materials and Methods: The research population comprised of participants who had symptomatic osteoarthritis of the knee according to the criteria established by the American College of Rheumatology (ACR). Seventy-six participants were randomly and equally distributed into two groups: the study group (oral diclofenac sodium) and control group (placebo). The participants in the study group were given one tablet of 50 mg diclofenac sodium and one tablet of vitamin B complex twice daily while those in the control group took only one tablet of vitamin B complex twice daily. Each participant in both groups took the drugs for seven consecutive weeks. The Statistical Package for Social Sciences (SPSS) version 20 software package was used for the data entry and analysis.
Results: Fifty-eight participants comprising of 19(32.8%) males and 39(67.2%) females completed this study. The male to female ratio was 1:2. There was a significant reduction in the knee joint pain intensity score in the study group at the end of seven weeks of treatment which was statistically significant (p=0.001) and also a statistically significant reduction in 30.4m walk-time of the participants in the study group (p=0.010), however there was no statistically significant change in the quadriceps muscle strength (p=0.056). There were no statistically significant changes in any of the outcome measures in the control group.
Conclusion: This study provides evidence to show that oral diclofenac sodium is efficacious in relieving symptoms in patients who have symptomatic KOA, when used with caution in selected patients at Nnewi.

Keywords: Efficacy; diclofenac sodium; knee joint pain intensity; quadriceps muscle strength; 30.4 metres walk-time.

1. INTRODUCTION

Diclofenac sodium is a non-selective, non-steroidal anti-inflammatory drug (NSAID) that is widely used therapeutically for its analgesic and anti-inflammatory properties in the treatment of KOA [1,2]. It prevents the biosynthesis of prostaglandins at both the peripheral and central levels by inhibiting Cyclo-oxygenase 1 and 2 (COX-1 and COX2) enzymes non-selectively [3]. Cyclo-oxygenase, an enzyme involved in the conversion of arachidonic acid to prostaglandins, exists in two isoforms: COX-1, a constitutive isoform, predominates in the stomach and produces cytoprotective prostaglandins, while COX-2, an inducible isoform predominantly involved in the inflammatory cascade, produces prostaglandins which give rise to articular pain, swelling, and stiffness. Diclofenac sodium is effective for decreasing pain and stiffness and improving function in symptomatic KOA [2,4]. However, it is associated with a high risk of gastrointestinal (GI) adverse events, such as bleeding, ulceration and perforation which can occur with or without warning symptoms [5]. There is increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those who are alcohol dependent, and those in poor general health [6]. Current evidence also suggests that use of diclofenac sodium is associated with increased cardiovascular risk [7], direct renal injury, including renal papillary necrosis [8], anaphylactic and serious skin reactions [9].

Diclofenac sodium is well absorbed following oral administration and undergoes first-pass metabolism. Only 50–60% of a dose reaches systemic circulation as unchanged drug and mean Peak plasma concentrations of 1.5 ug/ml (5 umol/l) are attained two hours following ingestion of 50 mg of diclofenac sodium [10].

Osteoarthritis (OA) is a chronic, complex, degenerative joint disease that the etiology bridges biomechanics and biochemistry. The primary pathology is cartilage destruction with joint space narrowing, osteophyte formation, subchondral sclerosis and synovitis [11]. Clinical manifestations of osteoarthritis include altered proprioception, muscle weakness and atrophy, pain, stiffness, and limitations in functional activities and social participation [12]. The knee is the most clinically significant site of primary osteoarthritis involvement [13] and by far the most common cause limiting the daily activities of the elderly population [14].

The severity of the disease is clinically scored according to pain and mobility indices while plain radiography remains the reference technique for assessing the severity of joint destruction. Because there are currently no disease-

modifying therapies, treatment is directed at managing OA-related symptoms which include pain, stiffness and joint swelling with a goal of minimizing functional impairment and improving quality of life. Non-pharmacologic treatments in the form of patient education, exercise, weight loss, and physical therapy can provide substantial benefits [15] but pharmacologic interventions constitute the most commonly prescribed therapy by healthcare providers [16] and commonly employed treatment by patients with KOA [17].

Osteoarthritis of the knee is one of the commonest orthopaedic conditions seen in the outpatient clinic and diclofenac sodium is commonly prescribed. There are many documented studies on the use of NSAIDS alone in the management of joint pain in KOA [18,19] but no scientific study has been carried out at Nnewi, southeastern Nigeria to determine the efficacy of oral diclofenac sodium in the treatment of symptomatic KOA. The purpose of this study was to determine the efficacy of oral diclofenac sodium in the treatment of symptomatic KOA in the local population using reduction in knee joint pain intensity, increase in quadriceps muscle strength and reduction in 30.4 metres walk-time as outcome measures.

2. MATERIALS AND METHODS

2.1 Study Design

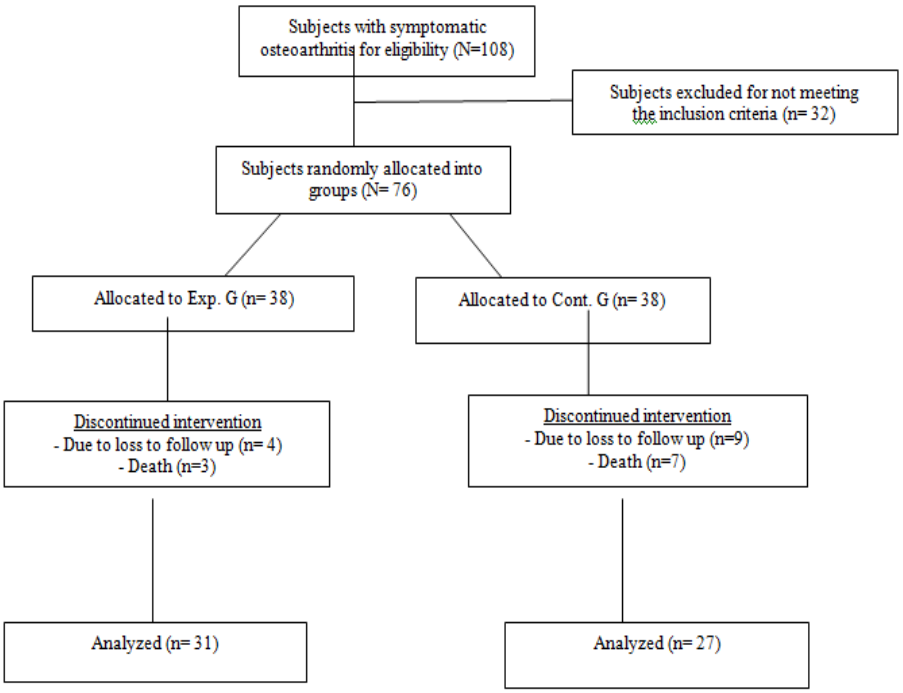
This study was a Randomized Controlled Clinical Trial.

2.2 Sample Population & Study Area

The research population comprised of participants who had symptomatic KOA according to the criteria established by the American College of Rheumatology(ACR) [20] at the orthopaedic outpatient clinic of the Nnamdi Azikiwe University Teaching Hospital, Nnewi.

2.3 Selection Criteria

Only participants who lived in the town where the hospital was located and were able to communicate clearly and walk without assistance were recruited into the study. Participants who had any form of inflammatory arthropathy, recent injury in the knee, history of peptic ulcer, heart disease, and known hypersensitivity to diclofenac, history of asthma, urticaria, or other sensitivity reactions precipitated by aspirin or other NSAIDS, pregnant or lactating mothers were excluded from the study.



Flow chart

2.4 Ethical Clearance

Ethical approval was obtained from the Ethical Committee of the hospital: certificate number NAUTH/CS/166/VOL.7/48 and all participants gave written informed consent for participation. The calculated estimated sample size was 242 using 19.6% prevalence for OA in Nigeria [21].

2.5 Study Procedure

The researchers could only recruit 76 eligible participants. They were randomly distributed into two groups: 38 participants into the study group (oral Diclofenac Sodium group) and 38 participants into the control group (placebo group). The sex, age, occupation, duration of knee pain, family history, social history and reports of plain radiographs of the affected knee(s) of the subjects were documented. Quadriceps muscle strength, 30.4m walk time (in seconds) and knee joint pain intensity were measured and recorded at beginning of the study for each participant.

Diclofenac sodium tablets (Olfen-50 Lactabs manufactured by Merckle GmbH, Blaubeuren-Weiler, Germany for Mepha LLC, Aesch-Basel, Switzerland) each containing 50mg of diclofenac sodium were used for NSAID therapy while vitamin B complex tablets (Manufactured by Emzor Pharmaceutical Industries Isolo-Lagos, Nigeria) each containing 1 mg of vitamin B1, 1 mg of B2 and 15 mg of Nicotinamide were used as the placebo drug. The recommended daily dose for long–term treatment of osteoarthritis was 75-100mg divided into 2-3 individual doses taken before a meal without chewing, together with a glass of water. A Stadiometer (SECA model) was used to measure the weights and heights of the participants while a stop watch (Nokia model, 8850), and inelastic measuring tape (bouncing rabbit, made in China) were used to record walk time and measure out the 30.4 metres walk distance respectively. The quadriceps muscle strength of the affected limbs was obtained using the Oxford Grading Scale [22] while Box Numerical Pain Scale (BNPS) of 1-10 was used to assess pain intensity [23].

The patients in the study group had one tablet of Olfen-50 Lactab and one tablet of vitamin B complex taken before a meal without chewing, together with a glass of water twice daily (morning and evening) while patients in the control group received only one tablet of vitamin B complex taken before a meal without chewing, together with a glass of water twice daily (morning and evening). The drugs were administered to each participant for seven consecutive weeks under strict supervision and monitoring. During the study period, all additional therapies such as topical NSAIDS, intra-articular corticosteroid injections and other analgesics were prohibited to be taken by the participants. At the end of seven weeks of treatment, the quadriceps muscle strength, 30.4m walk time (in seconds) and knee joint pain intensity were again measured and recorded. The study period was for one year.

2.6 Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 20 software package was used for the data entry and analysis. Descriptive statistics of mean and standard deviation were calculated for measurements taken. Paired samples t-test was used to compare pre and post test score changes for each parameter (knee joint pain intensity, quadriceps muscle strength and 30.4m walk-time) in each of the treatment groups. Alpha level for all statistical analysis employed was set at $p<0.05$.

3. RESULTS

Fifty eight participants completed the study. They comprised 19(32.8%) males and 39(67.2%) females. The male to female ratio was 1:2. The participants were within the age range of 45years and 80years, with a mean age of 54.02 ± 6.67 years. The mean weight, height and body Mass Index (BMI) of the participants were 84.47±7.89 kg, 1.74±0.03 m and 27.85±2.14 kg/m^2 respectively. The mean duration of condition was 2.79±1.28 years while the mean baseline pain intensity score, baseline quadriceps muscle strength and baseline 30.4 m walk time were 7.19± 1.26, 3.29 ± .46, 41.40 ± 7.22 seconds respectively.

Comparison of baseline demographic and clinical characteristics of the two groups given in Table 1; showed that more participants in the study group completed the study. Thirty-two participants in the study group completed the study while twenty-six participants completed the study in the control group. The mean age of 55.00 ±7.54 years, mean weight of 85.42 ± 7.85 kg and mean knee joint pain intensity score of 7.38±1.02 of the participants in the control group

were more than the mean age, mean weight and mean knee joint pain intensity score of the participants in the study group. However, the mean baseline quadriceps muscle strength of 3.41±.50 and mean baseline 30.4 m walk time of 42.18±7.58 sec were more in the study group. These differences were not statistically significant (p>0.05) except for the difference in baseline quadriceps muscle strength that was significant (p=0.031).

The means of the knee joint pain intensity scores of the two groups at beginning and at the end of the study showed that there was significant reduction in the knee joint pain intensity of the participants in the study group (p=0.001) at the end of seven weeks of treatment (Table 2). However, there was no significant reduction in knee joint pain intensity in the control group (p=0.170). Table 3 showed that there was no significant change in the quadriceps muscle strength of the participants in the study and control groups (p=0.056) and (p=0.33) respectively. There was a statistically significant reduction in 30.4m walk-time of the participants in the study group (p=0.010) but no significant reduction in walk-time of the participants in the control group (p=0.989) as shown in Table 4.

4. DISCUSSION

Osteoarthritis (OA), the third most common diagnosis in the elderly [24], causes significant pain leading to disability and decreased quality of life in affected individuals [25]. Researchers reported in a French study that more than 80% of clinical OA patients had limitations in activities of daily living; including basic tasks, work and leisure activities, and that these limitations affected patients who were retired as well as those still working [26]. Pain is the most debilitating symptom associated with symptomatic KOA in older adults. Pharmacologic interventions usually in form of NSAIDS especially diclofenac sodium constitute the most commonly prescribed therapy by healthcare providers [27] and are commonly employed by patients with KOA [28]. The decision to administer diclofenac sodium is usually made after carefully assessing and discussing the risk of gastrointestinal and other side effects with the patient. Patients with no risk factors are then prescribed the recommended dose of the drug and monitored for new symptoms and signs of gastrointestinal bleeding. Though diclofenac sodium has similar efficacy with other NSAIDS, it has one of the lowest risk profiles for gastrointestinal bleeding hence suitable in carefully selected patients [29].

The results of the study showed that diclofenac sodium significantly reduced pain. This is consistent with the results of other documented studies by other researchers [30,31]. There was significant and superior reduction in knee pain intensity in participants in the study group when

Table 1. Demographic and clinical characteristics of the two groups at baseline

Characteristics	Treatment groups		t-value	p-value
	Study	Control		
Number of participants	32	26		
Mean duration of Condition in years	3.03±1.28	2.5±1.24	1.592	.117
Male/Female	10/22	9/17		
Mean age (years)	53.22 ±5.87	55.00 ± 7.54	-1.012	.316
Mean weight (Kg)	83.69±7.96	85.42 ± 7.85	-.831	.410
Mean height (m)	1.73±0.03	1.75±0.04	-1.476	.147
Mean BMI (Kg/m^2)	27.79±2.18	27.93 ± 2.12	-.253	.801
Baseline pain Intensity score	7.03 ± 1.43	7.38 ± 1.02	-1.061	.293
Baseline quadriceps muscle strength	3.41 ± .50	3.15 ± .37	2.215	.031*
Baseline 30.4m Walk time in seconds	42.18±7.58	40.45 ± 6.76	.902	.371

Values are presented as the Means ± Standard Deviation
**Means p<0.05 is significant*

Table 2. Effect of diclofenac sodium on knee pain intensity

Treatment groups	Baseline PIS	PIS at end of study	t-value	p-value
Study	7.03±1.43	5.59±2.34	3.749	0.001*
Control	7.38±1.02	7.00±1.47	1.413	0.170

PIS means: pain intensity score, Values are presented as the Means ± Standard Deviation
**means p<0.05 is significant.*

Table 3. Effect of diclofenac sodium on quadriceps muscle strength

Treatment group	Muscle strength at baseline	Muscle strength at end of study	t-value	p-value
Study	3.41±0.50	3.59±0.50	-1.982	0.056
Control	3.15±0.37	3.19±0.40	-1.000	0.33

*Values are represented as the Means ± Standard Deviation, *means p<0.05 is significant.*

Table 4. Effect of diclofenac sodium on walk time

Treatment group	Walk time (in Sec.) at baseline	Walk time (in Sec.) at end of study	t-value	p- value
Study	42.18±7.58	37.79±5.44	2.744	0.010*
Control	40.45±6.76	40.47±7.30	-0.014	0.989

Values are presented as the Means ± Standard Deviation
**means p<0.05 is significant.*

compared with pain reduction in participants in the control group. Diclofenac sodium exerts its anti-inflammatory and antinociceptive effects both peripherally and centrally hence very effective in reducing pain in knee OA [32]. It has been shown to be highly effective for treating acute pain and remains one of the principal pharmacological agents for treating arthritic pain [33]. Published meta-analysis of 15 randomised clinical trials to assess the efficacy and safety of NSAIDs (ibuprofen, diclofenac, arthrotec, celecoxib, naproxen, rofecoxib) versus acetaminophen and versus placebo for treating OA involving 5,986 participants concluded that NSAIDs were superior to paracetamol for improving knee pain in OA [34]. From the results of the study, it appears that the vitamin B complex did not contribute significantly to pain reduction in the participants in both groups since there was no significant clinical and statistical reduction in pain intensity in the participants in the control group who were administered only vitamin B complex.

Participants in the study group did not demonstrate any statistically significant increase in quadriceps muscle strength probably because diclofenac sodium has no significant clinical effect in improving quadriceps muscle strength. In the search through the literature, the researchers did not find any study that suggested diclofenac sodium improved quadriceps muscle strength in individuals with KOA. Clinically, the results of this study suggests that physicians and orthopaedic surgeons should evaluate the prescription of diclofenac sodium as the only treatment in patients suffering from KOA because studies have demonstrated that quadriceps weakness and voluntary activation deficits are common occurrences in individuals with KOA when compared to age matched healthy controls [35,36]. Incorporating other modalities of treatment such as quadriceps muscle strengthening exercises which have been reported to increase quadriceps muscle strength and improve function in KOA [37] may enhance the efficacy of diclofenac sodium therapy.

At the end of seven weeks of treatment, oral diclofenac sodium produced a reduction in the 30.4m walk-time in the participants in the study group which was clinically and statistically significant. This may have been consequent to the pain relieving effect of diclofenac sodium as a result of its analgesic and anti-inflammatory properties resulting in improved function and performance. This is consistent with findings in previous studies by Ward et al. [2], Altman et al [28] and Small [38] who reported in their studies that diclofenac sodium was effective in reducing pain and improving function in the treatment of symptomatic KOA.

Traditionally, clinicians have relied heavily on the use of NSAIDs including diclofenac sodium to treat KOA symptoms of inflammatory pain, swelling and joint stiffness as numerous studies have proven these agents to be effective. Despite its side effects, diclofenac sodium still remains a drug of choice in the treatment of symptomatic KOA due to its proven efficacy and continues to be one of the most commonly prescribed and consumed analgesic/anti-inflammatory over-the-counter (OTC) drug. Clinical studies [30,39] have repeatedly demonstrated its efficacy, compared with placebo, in relieving pain and improving function in people with KOA as researchers have reported in this study.

5. CONCLUSION

Even as the number of patients with KOA continues to increase in Nnewi as a result of the increasing ageing population, treatment to manage the condition remains symptomatic, designed to control pain, improve function and quality of life while limiting adverse events. This study provides evidence to show that oral diclofenac sodium is efficacious in relieving symptoms in patients who have symptomatic KOA when used with caution in selected patients in Nnewi.

CONSENT

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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