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A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF ORAL DICLOFENAC AND DECREASED DOSE OF DICLOFENAC PLUS TOPICAL DICLOFENAC IN TREATMENT OF KNEE OSTEOARTHRITIS

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ABSTRACT: Objectives: To compare efficacy and safety of topical plus reduced dose of diclofenac to oral diclofenac in therapeutic dose. **Method:** The study was prospective, comparative and randomized, which included 50 patients suffering from knee osteoarthritis. Patients were randomized to receive either - oral diclofenac alone (50 mg thrice daily) (therapy1) or decreased dose of oral diclofenac and topical diclofenac (75 mg SR once daily + 10 mg Nanogel thrice daily) (therapy 2). The patients had been followed up for 7 days. Visual Analogue Scale and Lequesne Index has been used to evaluate the efficacy. Adverse drug reaction form, WHO and Naranjo Causality Assessment Scale were used to evaluate the safety of the patients. Data were analyzed by independent student t- test. **Results:** Out of 50 patients 17 were male and 33 were female. Osteoarthritis is more prevalent in 40-60 years of age, female patients and higher body weight and Body Mass Index (BMI). Therapy 2 was found statistically superior to therapy 1 on efficacy parameters (VAS Scale and Lequesne Index). Compliance was also better with therapy 2. **Conclusion:** Both therapies effective and well tolerated although therapy 2 is comparatively more effective and has more patient compliance than therapy 1. There was no ADR reported.

INTRODUCTION: Osteoarthritis (OA) is the most common form of arthritis, which affects millions of individuals aged 55 years and above, often leading to physical disability and reduced quality of life. [1-3] It is a late-onset musculoskeletal disease characterized by gradual thinning and loss of articular cartilage of the synovial joints with a concurrent alteration in the physiology of several other joint tissues, including the subchondral bone and the synovium. [2-6]

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Clinically OA is not one disease but a final common pathway secondary to many predisposing factors, most notably age, female sex, joint trauma, bone density, muscle weakness, altered biomechanics, and obesity. [7-9] Modifying these factors may reduce the risk of OA and prevent subsequent pain and disability. [8] Given the aging of the population and the increasing occurrence of obesity in our population, a major risk factor for disease, estimates suggest a doubling in prevalence from 2000 to 2020.[3]

OA can affect any joint, most commonly the knee, hip, spine, and hands.[7] Knee OA was the most common type affecting 6% of all adults. [9] The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater

than that due to any other medical disorder in the elderly. [9]

The number of OA cases rises in people of advancing age, possibly beginning as early as the third decade of life. As the population of elderly patients continues to grow, OA becomes a significant medical and financial concern and is expected to be a heavy economic burden on healthcare systems and community services all around the world.[10]

The rapid increase in the prevalence of this already common disease suggests that OA will have a moderate-severe impact on health care and public health systems in the future. [8] In OA patients, Health Related Quality of Life (HRQoL) and activities of daily living are also negatively affected. Significant work disability that is inability to do normal work, reduced ability to deal with household duties and sleep disorders are reported in patients with symptoms of OA flare-ups, together with dysfunctions in the areas of ambulation, body- care and movement and emotional behavior. [11, 12] Therefore, OA has a clear and detrimental impact on wellbeing, with up to one-fifth of affected individuals giving up work or retiring early because of the disease, and this increased morbidity contributes indirectly to an increased mortality.[4]

There is currently no cure for OA and treatment focuses on relieving pain and improving function of the affected joints.[1, 2, 5, 6] These goals should be achieved with minimal toxicity. [5]

Current recommendations for the management of OA include a combination of non pharmacological interventions and pharmacological treatments. Among these pharmacological treatments, non-steroidal anti-inflammatory drugs (NSAIDs), despite serious adverse effects associated with their long-term use, remain among the most widely prescribed drugs for OA. [6] Among NSAIDs diclofenac have an established place in the management of OA and related inflammatory disorders, while unable to modify the disease of OA; NSAIDs are frequently used chronically to manage symptoms. NSAID- related gastrointestinal (GI) adverse events (AEs), or "NSAIDs gastropathy", which result from decreased prostaglandin synthesis in the gastric lumen, and primarily affect older patients and women. [13] Oral NSAIDs also have other potential associated toxicities that must be monitored for and can limit the use of these drugs in certain populations including people of older age. [14]

Application of the topical diclofenac solution to the knee of patients with OA produced relief of symptoms equivalent to oral diclofenac, with minor local skin irritation, but significantly reduced incidence of diclofenac-related GI complaints and abnormal laboratory values. [15] Topical administration represents a useful alternative to oral treatment in the management of OA, especially in elderly patients and those at increased risk for serious gastrointestinal adverse events.[13] Topical application is also a method to increase the diclofenac concentration effectively in the muscle close to the body surface, which frequently presents inflammatory conditions due to overuse and trauma.[16]

This study was conducted with objective of analyzing efficacy and safety oral diclofenac Vs decreased dose of diclofenac and topical diclofenac in the treatment of knee osteoarthritis.

MATERIALS AND METHODS:

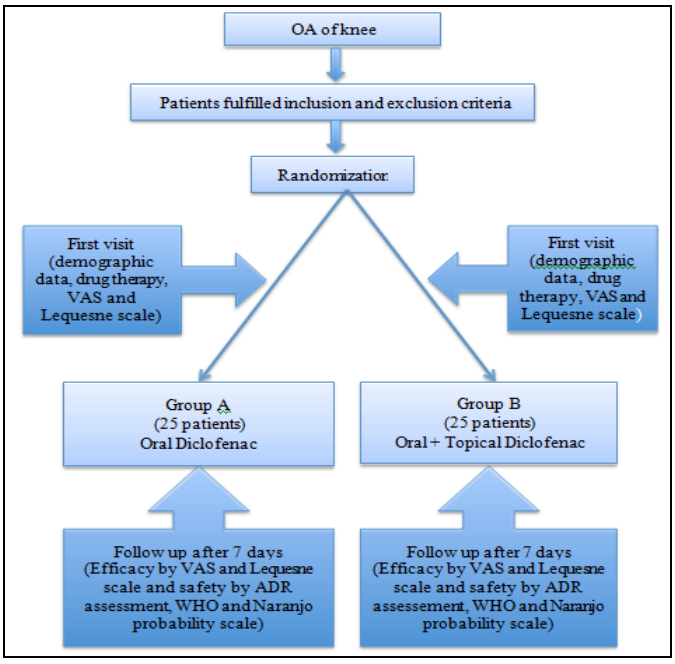
The study was prospective, comparative, randomized study, conducted in Shree Krishna Hospital affiliated to Pramukh Swami Medical College, a tertiary care teaching hospital in Gujarat, India. The study has been approved from Institutional Ethics Committee. Prior to enrollment informed consent has been taken for all the patients after explaining them objective of the study in their vernacular language.

All new male and female patients with age above 30 years diagnosed with OA of knee and who voluntarily gave their consent to participate in the study, were included in the study. Patients allergic to diclofenac, having psoriasis or any other inflammatory skin disease, with presence/ history of peptic ulcer, gastric bleeding and renal disease, pregnant and lactating women were excluded from the study. Study Duration was 4 months.

Patients were randomized in two groups consisting of 25 patients in each. In first group study drug Oral Diclofenac 50 mg t.i.d. (therapy 1) and in second group Oral Diclofenac 75 S.R. o.d. and Topical Diclofenac 10 mg Nanogel t.i.d. (therapy 2) were given. The respective therapies were prescribed for 7 days to both of the group of patients. The patients were followed up during their hospital visits after seven days. Successive measurement of pain score was carried out using Visual Analogue Scale (VAS) [17] and Lequesne Index 18 after a week of the treatment.

On the first visit. Demography details, personal history were noted. Patients were clinically examined and there were classified on the basis of severity of OA. On 1st follow up patients were asked for adverse drug reactions and scoring on both scales were noted. If the patient did not respond to the reduced dose of Diclofenac plus topical Diclofenac then the patients were immediately given the standard therapy that is the regular dose of diclofenec.

Statistical Analysis was done using independent student t-test.



RESULTS:

The study was carried out involving 50 patients having osteoarthritis from which one group involving 25 patients were given oral diclofenac 50 mg t.i.d. and another group involving 25 patients were given oral diclofenac 75 mg S.R. o.d. plus topical diclofenac 10 mg nanogel t.i.d. There are 17 males and 33 females out of total of 50 patients. Distribution of age has been divided in 5 groups (i.e.: 25-34, 35- 44, 45-54, 55-64, >65) with their gender.

All the age groups more number of female suffers from osteoarthritis of knee compared with males. Only 6 (12%) patients have suffered from OA of knees below 44 years of age. Data suggest that in female between the ages of 45-54 years risk of OA is more. As the age increases risk of OA also increases. Data suggest that in patients with age >60 years there is no difference in gender ratio, i.e. out of 12 patients of age >60 years the ratio of male and female is same. (**Fig.1**)

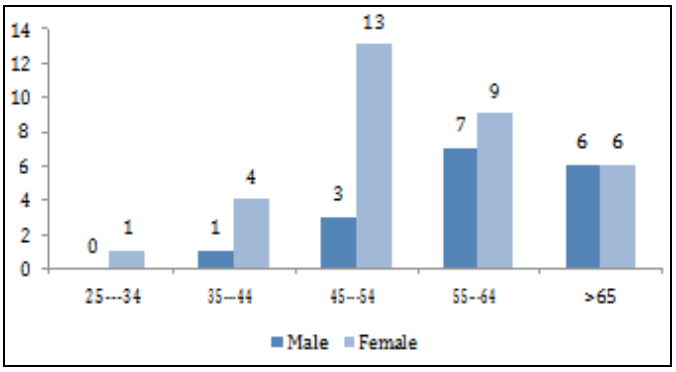


FIG.1: DISTRIBUTION OF AGE/ GENDER.

Out of 17 male patients only 1 (5.88) patient had weight <50 kg and the other 16 (94.12) patients had weight ≥50 kg. BMI has been divided in underweight i.e. <18.50, normal range i.e. 18.50-24.99, overweight i.e. 25.00-29.99 and obese >3 i.e. ≥30.00. Data shows that out of 50 patients 18 (36%) patients were overweight and 5 (10%) patients were obese and only 4 (8%) patients were underweight. (**Fig. 2**)

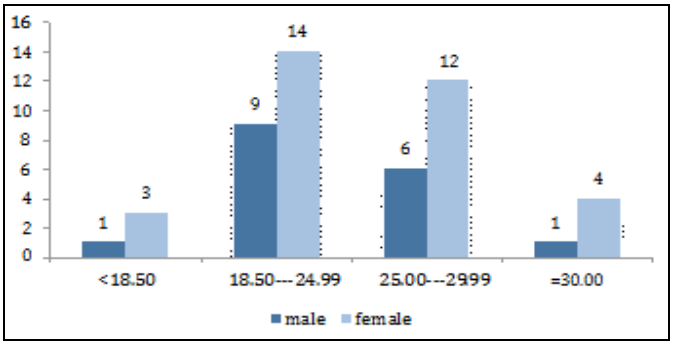


FIG. 2: DISTRIBUTION OF BODY MASS INDEX/GENDER.

Out of 50 patients suffering from OA of knee only 5 patients (10%) were having smoking habit. No patient was found consuming alcohol. O ut of 50 patients, 40 (80%) patients were consuming vegetarian diet and 10 (20%) patients were consuming mixed (vegetarian + non-vegetarian diet) diet. Data show that only 2 (4%) patients out of 50 patients experience early OA. Early OA is occurring at an early age i.e. ≤35 years of age. (**Table 1**).

TABLE 1: CLASSIFICATION OF PATIENTS ACCORDING TO SEVERITY OF OSTEOARTHRITIS

Diagnosis	Frequency
Early OA	2 (4)
OA of right knee	15 (30)
OA of left knee	8 (16)
OA of both knees	25 (50)
Total	50

TABLE 2: COMPARISON OF THERAPY 1 AND 2.

Sr. No.	Drug Therapy		Mean	N	Std. Deviation	Std. Error Mean	T
1.	Therapy 1: Oral diclofenac 50 mg t.i.d.	Pre VAS Score	6.80	25	1.41	0.38	10.21
		Post VAS Score	2.96	25	1.24		
		Pre Lequesne Index	9.12	25	1.93	0.52	8.97
		Post Lequesne Index	4.44	25	1.75		
2.	Therapy 2: Oral diclofenac 75 mg S.R. o.d. plus topical diclofenac 10 mg nanogelt. i.d.	Pre VAS Score	6.40	25	1.29	0.32	14.55
		Post VAS	1.80	25	0.91		
		Pre Lequesne	8.22	25	1.95	0.48	9.55
		Post	3.60	25	1.44		

Analysis of oral diclofenac 50 mg t.i.d. and oral diclofenac 75 mg:

S.R. o.d. plus topical diclofenac 10 mg nanogel t.i.d. with independent t -test (Small group correlated group) was done using VAS Scale and Lequesne Index. Data show that there is a significant difference observed before and after therapy in both the drug therapies proving that both the therapies are effective in the treatment of knee osteoarthritis although therapy 2 is slightly more effective than therapy. (**Table 2**)

TABLE 3: COMPARISON OF THERAPY 1 AND 2 IN MALE AND FEMALE

Sr. No.	Drug Therapy	Sex		Mean	N	Std. Deviation	Std. Error	T
1.	Therapy 1: Oral diclofenac 50 mg t.i.d.	Male	Pre VAS Score	6.36	11	1.68	0.63	5.00
			Post VAS Score	2.72	11	1.27		
			Pre Lequesne	8.45	11	1.98	0.84	5.30
			Post Lequesne	4.00	11	1.96		
		Female	Pre VAS Score	7.14	14	1.09	0.44	9.06
			Post VAS Score	3.14	14	1.23		
			Pre Lequesne	9.64	14	1.79	0.63	7.66
			Post Lequesne Index	4.79	14	1.55		
2.	Therapy 2: Oral diclofenac 75 mg S.R. o.d. plus topical diclofenac	Male	Pre VAS Score	5.66	6	1.21	0.60	6.93
			Post VAS Score	1.50	6	0.83		
			Pre Lequesne	8.08	6	1.46	0.73	6.50
			Post Lequesne	3.33	6	1.03		
		Female	Pre VAS Score	6.63	19	1.25	0.36	13.17

10 mg nanogel t.i.d.	Post VAS Score	1.89	19	0.93		
	Pre Lequesne	8.26	19	2.11	0.60	7.61
	Post Lequesne Index	3.68	19	1.55		

Table 3 shows the mean score of VAS Score (before and after drug therapy) and Lequesne Index (before and after drug therapy) of both the therapies 1 and 2 in males and females. Data show that there is a significant difference observed before and after therapy in both the drug therapies in males and females proving that both the therapies are effective in the treatment of knee osteoarthritis. Data show that in males and females both the therapies are effective although therapy 2 is more effective.

TABLE 4: COMPARISON OF THERAPY 1 AND 2 IN PATIENTS WITH AGE <60 YEARS AND PATIENTS WITH AGE ≥60 YEARS

Sr.	Drug	Age		Mean	N	Std.	Std.	T
1.	Therapy 1: Oral diclofenac 50 mg t.i.d.	<60	Pre VAS Score	6.63	16	1.50	0.48	7.96
			Post VAS Score	2.75	16	1.24		
			Pre Lequesne	9.00	16	2.14	0.64	6.60
			Post Lequesne	4.65	16	1.52		
		≥60	Pre VAS Score	7.11	9	1.26	0.58	6.42
			Post VAS Score	3.33	9	1.22		
			Pre Lequesne	9.33	9	1.58	0.87	5.97
			Post Lequesne	4.05	9	2.12		
2.	Therapy 2: Oral diclofenac 75 mg S.R. o.d. plus	<60	Pre VAS Score	6.21	14	1.25	0.40	11.34
			Post VAS Score	1.64	14	0.84		
			Pre Lequesne	7.60	14	1.82	0.60	6.96
			Post Lequesne	3.35	14	1.37		
		≥60	Pre VAS Score	6.63	11	1.36	0.50	9.10
			Post VAS Score	2	11	1.00		
	Topical diclofenac 10 mg		Pre Lequesne	9.00	11	1.89	0.72	6.95
			Post Lequesne	3.90	11	1.51		

Table 4 shows the mean score of VAS Score (before and after drug therapy) and Lequesne Index (before and after drug therapy) of both the therapies 1 and 2 in patients with age <60 and patients with age ≥60. Data show that there is a significant difference observed before and after therapy in both the drug therapies in patients with age <60 and patients with age ≥60 proving that both the therapies are effective in the treatment of knee osteoarthritis. Data show that in patients with age <60 and patients with age ≥60 both the therapies are effective although therapy 2 is more effective in patients with age <60 and patients with age ≥60.

Safety Analysis:

There were no adverse drug reactions recognized as such because the patients were already prescribed either H2 Receptor Blocker or Proton Pump Inhibitors with the therapy.

DISCUSSION: It indicates that females are at more risk of osteoarthritis than males. In this study prevalence rate of female suffering from OA is 66% and for male it is 34%. Prevalence of OA is almost double than male in the study. Dulay et al.[9] confirmed that females are twice more likely to be affected than males. Another study conducted by Yuqing Zhang et al.[8] showed that OA is more prevalent in women (13%) than in men (10%).

Therefore we conclude that sex is a major risk factor for the patients with knee osteoarthritis. Yuqing Zhang et al. concluded that people affected with symptomatic OA is likely to increase with the aging of the population.[8] A. Mobasheri confirmed that advancing age is a major risk factor for degenerative joint disease.[19] Therefore we conclude that age is one of the strongest risk factor for the patients with knee osteoarthritis.

Data shows that there are very few males and females affected with weight less than 50 kg. Data show that more number of males and females are affected as the weight increases i.e. in patients with weight ≥50.

Yuqing Zhang et al.[8] concluded that obesity and overweight are potent risk factors for OA, especially OA of the knee. Farshid Gulik [20] confirmed that obesity could increase the risk as well as progression of OA. Therefore we can conclude that weight is a major risk factor for the patients with knee osteoarthritis.

Data show that more number of males and females are affected as the BMI increases. Yuqing Zhang et al.[8] concluded that obesity and overweight are potent risk factors for OA, especially OA of the knee. Therefore we can conclude that BMI is a significant risk factor for the patients with knee osteoarthritis. M. Blagojevic [21] concluded that smoking has no effect on OA of knees. This suggests that smoking habit and OA does not have any relation. Data show that OA of right knee is more common than OA of left knee as well as OA of both knees. Joern W. P. Michael et al.[22] conclude that knee OA in men is more common in right knee and it is evenly balanced in both the knees in women.

Bindu Nair et al.[14] concluded that topical targeted delivery of diclofenac had decrease systemic absorption and therefore had limited systemic toxicity without sacrificing local effect and benefit i.e. it has the same benefits as that of oral diclofenac eliminating the serious side effects that are related to oral diclofenac. Lee S. Simon et al.[23] concluded that addition of a topical diclofenac to oral diclofenac did not increase the incidence of systemic adverse effects and that topical diclofenac is an effective treatment option for knee OA with efficacy similar to, but tolerability better than oral diclofenac.

Niklas Schuelert et al.[24] concluded that topical diclofenac shows promise as an effective means of controlling OA pain and appears to be a safer alternative to oral NSAIDs. Tugwell PS et al. [15] concluded that application of topical diclofenac to the knee of patients with OA produced relief of symptoms equivalent to oral diclofenac. McPherson ML et al.[25] concluded that topical diclofenac solution provides 6-week relief of the symptoms of knee OA. Gregor Cevc et al.[26] concluded that topical diclofenac formulations are more efficacious than oral diclofenac. Arthur A.M. Bookman et al.[27] concluded that topical NSAIDs are an alternative to oral treatment with reduced side effects. Martin Brunner et al.[28] concluded that topical diclofenac offers an alternative to oral diclofenac formulation.

John H. Peniston et al.[29] suggested that by decreasing the NSAIDs dose by including topical NSAIDs might prevent the risk of drug- drug interactions that could lead to adverse events. The data showed the correlation with the above-mentioned studies. Therefore it showed that in this study that topical diclofenac is more efficacious than oral diclofenac and is a useful alternative to oral diclofenac.

Limitation: The limitation of this study was that the numbers of participants were less and the duration of the study was short. Patients were followed for only seven days so the long- term effects of the therapy could not be concluded.

CONCLUSION: Age, Sex, Weight, Body Mass Index are the major risk factors associated with Osteoarthritis of knee. Both therapy 1: Oral Diclofenac 50 mg t.i.d. and therapy 2: Oral Diclofenac 75 S.R. o.d. and Topical Diclofenac 10 mg. Nanogel t.i.d. are effective and well tolerated although therapy 2 is comparatively more effective than therapy 1.There are no ADR found in any case may be due to the smaller size of subjects as well as the duration of the study is less.

In future there is possibility to do extension of this study to find out the ADRs between two therapies in longer duration of time with more number of subjects.

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