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TO COMPARE THE SAFETY AND EFFICACY OF ACECLOFENAC VS. ACECLOFENAC PLUS DIACEREIN IN KNEE OSTEOARTHRITIS PATIENTS

Clinical Research

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ABSTRACT

BACKGROUND- Knee OA is the second most ordinary long-term degenerative rheumatologic disease affecting over 180 million people in India, accompanied by severe pain followed by functioning restrictions and wellbeing. Knee OA affects the knees making the patient physically disable to perform normal activities. Present study is performed to investigate all the factors affecting knee OA patients walking speed with respect to aceclofenac plus diacerein. **MATERIALS AND METHODS –** Questionnaire based study was conducted with 50 patients at Dr. RML Hospital, New Delhi. The control group was given Aceclofenac 100 mg twice a day plus placebo for 1 month. The test group was given Aceclofenac 100 mg twice a day plus tab Diacerein 50 mg for 1 month. The t-test statistical method was applied with <0.05 p-value to perform this study. **RESULT AND CONCLUSION-** The test group (aceclofenac 100 mg + diacerein 50 mg) was found to be more effective than the control group (aceclofenac 100 mg + placebo). Aceclofenac plus diacerein combination is found safe for the treatment of Knee OA. Face rating scale (FRS) has shown that 20% of the test population was suffering from mild symptomatic pain, 22% of them were facing moderate pain, 24% of them have accepted painful episodes and similarly the major test population (30%) has confirmed their knee OA experience as an extreme painful crisis. These were suffering from extreme pain, swelling and stiffness at the knee joints before the treatment. The symptom intensity was recorded to be decreased after providing the medication for a month.

KEYWORDS

Knee osteoarthritis, WOMAC, Aceclofenac, VAS, Diacerein.

INTRODUCTION

OA is a persistent bone and joint disease which affects the bones, cartilage and the synovium presented in the knee joint, presented clinically as joint pain, swelling, stiffness and loss of movemenent. The synovium is the soft tissue lines at the tendon sheaths and joints. It produces synovial fluid which acts as lubricating agent, supplies nutritients and O_2 to the cartilage. It is essential to repair the affected joint to maintain the gesture impaired by so many traumas or accidents. Knee OA is the principle origin of movement disability among women. OA is also termed as degenerative joint disease (DJD).

GAS test is done to assess the patient's pain in terms of worst or bad. Numerical measurements are enigmatic. GAS test, being reliable and authenticated, measures the patient's Global Impression of Change (PGIC) with reference to ache, performance & standards of living allowing the patients to unite all the factors in addition to answer the foremost clinical cross-examining. OA mainly acts on the synovial joints and is identified by advancement of the articular cartilage decay along with subchondral bone modification, synovial membrane inflammation, sclerosis of the subchondral bone and osteophyte generation. These changes are elevated as the disease progresses. Due to these elements, the current research work was conducted in order to assess the clinical potency of diacerein together with aceclofenac.

OA pain reduces a person's daily activities by altering the ability to perform their routine tasks and can be the vital conclusion of OA. OA in contrast with knee, hip and hands, illustrate a harmonious growth-related prevalence rate. The frequency of OA development rises with the rising. [1]

The prime objective in OA management is to minimize symptoms, functional impairment, restrain the anatomical alteration and arthoplasty. NSIADs are provided to lower down the painful crisis as they are not able to alter the disease progression.

The actual prevalence of OA is laborious to find out because the clinical signs of OA do not always communicate with the anatomical alteration. Radiography seems to be more complex due to various sensitive imaging techniques including magnetic resonance imaging (MRI), computerized tomography signifying anomalies discovered by X-rays.[2]

Clinically, the prime target of OA management involves pain control, governing the movement span followed by the affected joint strength and restricting the functional disability.[3]

Diacerein is anthroquinoline derivative which inhibits IL-1β, delaying all biological process commencing in OA. Diacerein is proven to be equally analgesic effective as compared to Aceclofenac in the patient of OA knee. In adults more than 45 years, ordinary joint pain area lasts up to a week in previous month is in the knee (19%) , maximum prevalence is observed in the women aged more than75 years (35%).[4]

OA Pathophysiology

OA origin is dependant to various interactions including increasing age, hereditary, abrasion, knee displacement, enhanced biomechanical strain due to obesity, enlarged bone density and physiological process imbalance. Obesity is found to be the new evidence displaying neuroendocrine and pro-inflammatory pathway progression leading the modified food intake control, lipid expression and vitality alterations. The synthesis of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-18 and TNF alpha) is stimulated by the restorative white adipose tissues. Leptin, the obesity gene found in synovial joints, may have importance for the progression and onset of OA.

The modification process in joint begins in distinction with subchondral bone expression, bone marrow lesions, meniscal tears and extrusion, then cartilage defects leading to cartilage damage and finally radiographic OA. Evidence reveals menisci, ligament, and particularly the joint capsule's involvement in the development of knee OA.

Risk factors for Osteoarthritis:

- Genetic 40-60%
- Ageing

- Female gender
- Obesity
- High bone density
- Joint injury,
- Reduced muscle strength,
- Joint laxity,
- Joint displacement

Joint Pain:
It is the result of increasing age, overweight, etc. An estimated report suggests that 8.5 million people in the UK are suffering from joint pain. It can be a result of joint pain caused by bursitis, tendonitis, etc.[5,6]

Radiographic Osteoarthritis:
Radiographic OA is found to be higher in women than men, affecting about 25% of the population aging 50 year and over.[7,8] Severe pain and loss of mobility was reported by more than 23%, hand pain by 12% of the test population in adults with 45 year age and over 30% in adults with 50 year age.[9,10]

The Relationship between Symptomatic and Radiographic OA:
A uniform relationship can be seen between these two variables in terms of stiffness, intensity and physical performance limitations. 50% of the population with 50 or more than 50 years of age has similar symptoms of the 25% geriatric patients 66% of the population has radiographic OA.[11]

Prevalence in Geriatric Patients
In Asia and Africa, OA of hip seems to be less common than in the Western countries. Gender differences are observed with a higher prevalence in females during the menopausal stage. Asian women with average menopausal age of 46.3 years are at early risk of OA than that of Western women with 51 years age. Apart from aging and gender other etiological factors of OA described as nature of work, physical activities, community lifestyle and obesity.

In case of India, OA prevalence is 56.6% and females are more susceptible to develop OA as compared to males (70.1% vs. 41.6%). With 22%-39% prevalence rate in India, OA is considered as succeeding rheumatologic problem. On average 45% women over 65 years have symptoms at the same time radiological evidences were grounded in 70% women with 65 years age. OA prevalence is reported to be in the range of 17%-60.6% in India. Symptomatic knee OA is developed in the population (13% women and 10% men) more than 60 years.

OA develops more frequently in females aged more than 55 years age. All the races are found to be affected uniformly in USA. Japan has a higher incidence rate of OA development while east Indians, southern Chinese and African blacks have minor rates. OA is not associated with a known cause, hence called as secondary OA.[12]

Development Stages:
Knee OA takes a few years to develop in various stages. The treatment is hard to employ because the symptoms are not properly appeared. The medication is started only when the OA reaches a leading phase.[13-15]

Minor: - Osteophytes are the small lumps of bone growing in the knee, can damage slightly to the cartilage. There is no evidence of synovial cavity narrowing. The patients may feel slight pain and discomfort may be experienced in the beginning. The joints are found to be natural on radio diagnosis.

Mild: - The patient may feel symptoms and the physician may observe a few signs of wearing. All the scans reveal the osteophyte growth and cartilage loss. The synovial cavity still appears to be normal but the joints will start to be consolidated.

Moderate: - The cartilage damage has progressed, the synovial cavity is narrowed and cartilages loss can easily be displayed on radiography. Pain and discomfort may be experienced performing routine works. The cartilage is continued to thin and breaking down with progressing OA.

Severe: - In severe OA situations, knee replacement surgery is the only option left. The synovial space continues to narrow, resulting in cartilage destruction. Consequently, joint stiffness is increased with unvarying burning sensation and fluid loss throughout the joint. Bone overlapping can be seen in radio diagnosis.

Origin of Osteoarthritis
The idiopathic OA, not triggered by an injury or disease, is somewhat an outcome of natural decay of joints. Cartilage degeneration is initiated by tinny flakes formation. When a damaged joint is kept in practice for a long period, the cartilage is mechanically irritated and inflammation is seen over the organ resulting in joint pain and swelling. OA sometimes develops in more than one member of the same family, implying a hereditary basis for knee OA.[16] Overweight is not a good factor in contrast with knee and joints as it increases the stress on the joints, as the age increases chances of OA development are also increased. The ligaments, bones, and cartilage trauma is considered responsible variable to pilot the early knee OA. It is usually seen in football players and defense personnel. Uric acid crystals may initiate arthritis in gout and calcium pyrophosphate crystals induce arthritis in case of pseudogout.[17-19]

Diagnosis of OA
During the physical examination, the physician closely examines the damaged joint, investigate the redness and for the dimension of locomotion in the joints. Diagnosis includes: [20]

- **X-ray Reports-** An X-ray report may also display bone spurs throughout the joint. Some patients may represent an X-ray evidence of OA as sooner they sense any manifestation.[21]
- **MRI- R**adio waves and a firm magnetic field is used to generate a detailed illustration of bones, soft tissues and cartilage.
- **Synovial Fluid Assay-** An orthopedic surgeon collects the synovial fluid sample with the help of a needle in order to check for any inflammation around the synovial cavity resulted by gout/infection.
- **Hematology-** It helps to eliminate the actual cause of joint pain in case of rheumatoid arthritis**.**
- **Sign snd Symptoms of OA**
- **Stiffness-** Stiffness is the familiar sign in case of OA experienced by the patients in the early morning or after a long inactive interval. This situation is typically sorted out by a light body movement or physical activity and takes up to 30 minutes to warm the joints for a slight mobility.
- **Rigidity-** Muscle hardness can be experienced by the patient with absolute mobility failure.
- **Inflammation-** It can be a result of excess fluid accumulation, clinically referred to as effusion. The joints may feel warm by touch if the swelling is severe.
- **Cracking-** In this situation the patient experiences the grinding of two joints with other during movements because of the joint articulation. Joint is felt to be warm due to lots of friction.
- **Osteophytes-** Points of the bone developing outwards the joint caused by the joint friction.
- **Deformity-** Physical deformity can be seen in terms of augmented finger joints as a result of friction.

Types of OA

- **Post traumatic knee arthritis-** This type of OA is developed after tendon abrasion. The depletion of cartilage may be enhanced but the injured part is healed speedily.
- **Rheumatoid arthritis-** It falls under an autoimmune disorder category. It is a layer of connective tissues lined with tendon sheath. Knee pain can be an outcome of rheumatoid. It causes the joint inflammation; knee feels swollen, stiff, warm and painful.[22]
- **Psoriatic arthritis-** The patient may feel knee pain, stiffness, swelling and tenderness, when affected by psoriatic arthritis. The fingers and toes are frequently affected.
- **Gout-** A type of inflammatory arthritis responsible for uric acid crystals (monosodium urate crystals) accumulated in the knee joint. Tinny needle-like crystals are found in the soft muscles which can be responsible for the joint pain, swelling, redness and warmth.[23,24]
- **Reactive arthritis-** It is a result of immune response against an infection like sexually transmitted disease (STD). Symptoms may develop pain in various joints and inflamed eyes.

Treatment Strategy
The therapy depends upon the OA severity and disease progression.

Mild
The symptoms are conventionally negligible, paracetamol or other mild analgesic medicament may be applied to relief the pain. Slight exercise is able to attain vitality and adjustability.[25]

Moderate

- Pain killers
- Exercise is recommended for the maintenance of hardness and limberness.
- Put on knee brace to reduce the pain intensity at the joint.[26]

Severe
- Taking OTC pain killers.
- An administration of prescription analgesic agents like oxycodone and codeine.
- Corticosteroid injections to minimize inflammation and swelling at the joint.[27]

Extreme
- The extreme symptoms of knee OA represent complete cartilage failure and the patient is suggested for knee joint replacement surgery.

Non- Pharmacological Treatment Strategy
- Acupuncture
- Magnetic pulse therapy
- Lateral-wedge insoles to be worn inside of the shoe
- Glucosamine supplements
- Needle rinsing.

Stem Cell Remedy
It is still a mystery for the researchers whether stem cell therapy is able to redesign the damaged cartilage in knee OA patients. This could be unproductive for the patient having a BMI more than 35. This procedure is costly and the patient needs to face various trials to obtain a desired result.

Side Effects:
- ADR at the site of injection
- Dislocated cell regeneration
- Unwanted cell functioning
- Likelihood to develop tumor

Prevention
Balanced Weight Maintenance
Additional weight puts an extra force on the knees, contributing to cartilage damage. It also prompts the body to build extra cytokines leading to inflammation. It may misguide the cartilage to work naturally.

Glycemic Control
Elevated glycemic levels may alter the cartilage organization and its activity which can be experienced in case of diabetes. Sometimes cartilage damage is also reported.

Regular Exercise
It can be helpful in order to keep the joints flexible, increasing muscle strength and lowering the swelling. Gardening, swimming, walking, etc can be better activities done for 30 mins, 5 times a week.

Reduced Injury Risk
Increased body weight increases the stress at weight-wearing joints of the body like knee. It is advisable to minimize chances of home trapping. One should put on shoes and use preventive gears while performing physical activities to avoid any kind of injury.

Position and Bone Calibration Tests
Knee OA affects the joints majorly which is responsible for the body's normal posture. GAIT test deals with the systemic study of human locomotion property. It helps to determine the severity of knee OA development.

Avoid Over-Weight Lifting
Over weight may contribute to impart excess stress on joints. Weight-lifting athletes normally lift heavy weight and are more prone to have an advancing chance of OA development. Frequent knee movement can be seen in almost sports activities contributing to imparting pressure on joints in the form of squatting and kneeling.

MATERIALS AND METHODS
Study Site and Duration:
The research was organized after getting an ethical approval from the Institutional Ethical Committee of Dr. Ram Manohar Lohia Hospital, New Delhi. All the study participants were recruited from PMR, OPD, Dr. Ram Manohar Lohia Hospital, New Delhi. Duration of the study was 3 months.

INCLUSION CRITERIA:
- Patients aged with 18-60 years.
- Patients with Knee joint osteoarthritis diagnosed by the physician on the basis of radiology diagnosis Kellgren-Lawrence Grade II or III severity (American College of Rheumatology).

EXCLUSION CRITERIA:
- Patients <18 and >60 years.
- Patients with peptic ulcer, hepatic, septic arthritis, gout/acute knee trauma and renal disorders.
- Patients received NSAIDs in previous treatments. Ongoing therapy with suggestive moderately acting OA medicines: chondroitin sulphate and diacerein.
- Patients having a known hypersensitivity/contraindication for aceclofenac or diacerein.

Study Groups:
- **Control group:** Aceclofenac 100 mg tablet twice a day for 1 week + placebo for 1 month.
- **Test group:** Aceclofenac 100 mg tablet twice a day for 1 week + Tab. Diacerein 50 mg for 1 month.

Sample Size Calculation:
The sample size was determined as a minimum of 15% favorable improvement in the WOMAC score after intervention with Aceclofenac and Diacerein drug and comparative analysis required with 95% confidence level. The sample size was determined to be 50 patients suffering from OA by employing t-test as the statistical measurement.

Subject Randomization & Dose Administration:
Patient allocation in all the subgroup was in the ratio of 1:1 and all the subjects received Aceclofenac 100 mg tablet daily for 1 week and SOS up to a month. Diacerein 50 mg in the test group was taken once a day up to one month with the main meal.

Subject Pain Analysis:
Womac Arthritis Index:
WOMAC is a set of 24 questions classified in terms of pain, stiffness and function with 96 points. If there is no problem each question is given zero, mild problems-1, moderate problems-2, severe problems-3 and extreme problems-4. The peak WOMAC count suggests an imperfect outcome while the lesser outcome is believed to be outstanding.

Visual Analysis Score (VAS)
VAS (numeric rating scale) was employed with children more than 10 year and adults. VAS possesses two outcomes ranging from 0-11. Numeric value with zero represents no pain and 11 represent the worst possible pain.

Biochemical Measurement:
- Serum calcium and vitamin-D levels,
- CBC, KFT & LFT

Data Management:
The data was recorded at a predesigned Performa. The data entries were done on MS Office Excel Spreadsheet.

Statistical Data Investigation:
Statistical package for the Social Sciences (SPSS) software was utilized for the analysis of data. An average WOMAC and pain scores and Aceclofenac vs. Diacerein before treatment were set against using t-test and p-value of <0.05 was taken.

Steps For Subjects Withdrawal for Safety Issues:
- All the subjects not willing to participate in the study any further, will withdraw from the study.
- Subjects exposed to any clinical or biochemical side effect due to any investigational drug or any related adverse event will be withdrawn from the study and will be referred for standard treatment.

RESULT AND DISCUSSION
Cohort Study:

Total 50 patients were included in the study. Demographic characteristics including their age and gender are shown in Table 1. According to the data, females (66%) are more prone to develop OA as compared to males (34%). More problems were seen in the old age patients (mean value: 48.22 years).

WOMAC OA INDEX:

Womac scale is consisted of questionnaires to assess OA patients regarding pain, stiffness and physical functioning. Womac score is distributed as pain (0-20), stiffness (0-8) and functional limitation (0-68). The peak WOMAC count suggests an imperfect outcome while the lesser outcome is believed to be outstanding. The outcome is classified according to the values as: excellent <14, good: 15-28, fair: 29-38 and poor :> 38 points.

Table- 1. Disease Prevalence

Variables	Radiographic	Symptomatic
Knee	**25%**	**13%**
Hip	**11%**	**5%**
Hand	**41%**	**3%**

Table- 2: Patient Demographics

Group	Group-A (N-25)	Group-B (N-25)	Total (N-50)
Age (35-45)	**8 (32%)**	**7 (28%)**	**15 (30)**
Age (46-60)	**17 (68%)**	**18 (72%)**	**35 (70)**

Table- 3: Womac Questionnaire

Variables	None	Mild	Moderate	Severe	Extreme
Bending	**1**	**9**	**14**	**20**	**6**
Walking on a flat surface	**2**	**7**	**14**	**21**	**6**
Getting in/out of a car	**15**	**13**	**11**	**6**	**5**
Going shopping	**1**	**4**	**8**	**12**	**25**
Putting on/off socks	**18**	**11**	**10**	**7**	**4**
Getting in/out for bath	**1**	**7**	**10**	**28**	**4**
Having domestic duties (Bag lifting)	**0**	**3**	**5**	**10**	**32**
Light domestic duties (Cooking)	**1**	**3**	**6**	**14**	**26**
Getting in/out of the toilet	**1**	**3**	**10**	**29**	**7**

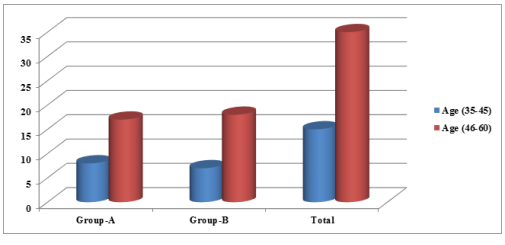

Fig. 1: Age Distribution Graph

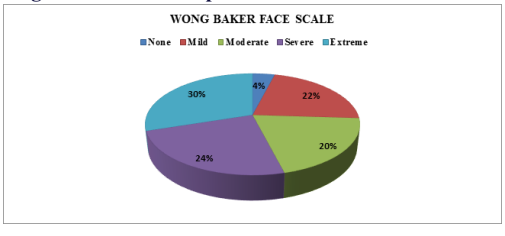

Fig. 2: Face Rating Scale

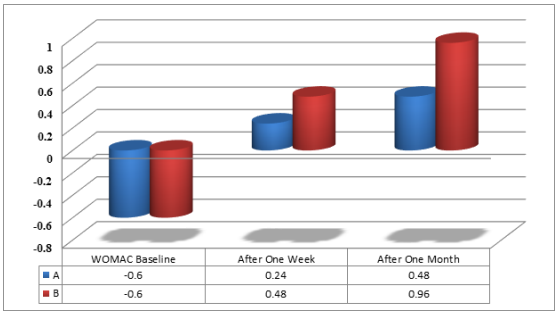

Fig. 3: Global Assessment Scale

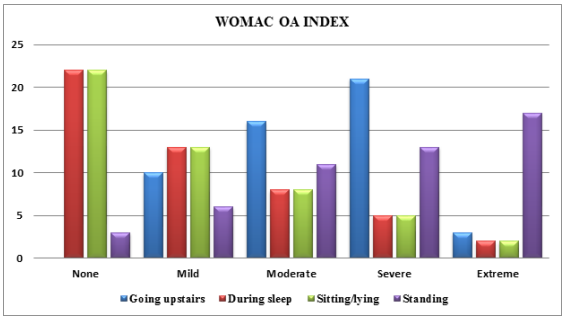

Fig. 4: Womac Oa Index (pain Analysis)

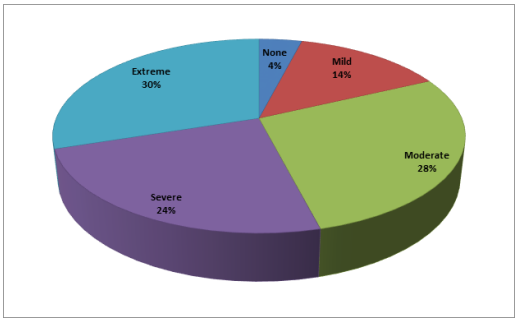

Fig. 5: Womac Oa Index (knee Stiffness Analysis)

CONCLUSION

Knee OA patients are more prone to face physical disability and more severe problems while performing normal activities like bending, walking, shopping, toilet use, using the stairs and lifting heavy and light domestic stuffs. This study was conducted to check every possible aspect faced by knee OA patients in their daily life by comparing the safety and efficacy of aceclofenac vs. aceclofenac and diacerein combination. The result obtained from the research study is divided into tabulation and the graphical representation. The prevalence of radiographic and symptomatic OA has shown with three variables namely Knee (25%), Hip (11%) and Hand (41%) [Table 1]. Patient demographics are represented in two age groups with an equal number of participants (25 patients in each group), group-A ranging from 35-45 years and group–B ranging from 46-60 years of age [Table 2]. Pain intensity was determined by the use of face rating scale on the basis of the data provided by the patients according to the pain category. The pie chart represents the pain extent in terms of percentage and is categorized into the respective pain category. Accidental cases and injury from various reasons are termed as severe and extreme pain categories [Figure 2]. Global Assessment Scale represents the WOMAC baseline vs. one week/one month response in both the groups. Group-B represented maximum improvement with a value of 0.96 [Figure 3]. Pain analysis was done by using WOMAC OA Index. Bargraph represents four variables including use of stairs, during sleep/rest, Knee stiffness during lying in bed & standing for a long time [Figure 4]. Knee OA patients suffer from the knee inflammation, swelling and stiffness. It was also assessed during the research work. On the basis of the patient's response a pie chart was constructed to show the actual data in terms of percentage. Most of the patients have complained about the pain experienced during daily life activities like walking on a flat surface, during the bath, sleeping, bending, use of stairs, shopping, toilet use and heavy and light stuff lifting. The majority of the response lies between moderate (28%), severe (24%) and extreme pain (30%) [Figure 5]. The final impression includes pain severely/extremely experienced by the patients during bending, stairs use, standing for a long time, during toilet use & during sitting. At the final impression, we got to know that, pain and stiffness assessment, performed in the term of bending (40% severity), walking on a flat surface (42% severity), shopping (50% extreme), getting in/out for the bath (56% severity), heavy domestic duties (64%), light domestic duties (52% extreme) and use of the toilet (58% severity) were found during the pain assessment in terms of severity and an extreme pain experienced by the patients [Table 3].

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