

Comparison Of Diacerein-Ginger With Diacerein Alone In Treating Knee Osteoarthritis

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ABSTRACT

Objective: To compare clinical efficacy of diacerein-ginger with diacerein alone in treating knee osteoarthritis.

Duration and place of study: It was a randomized clinical trial conducted from 21st September 2018 to 31st March 2019, in medical OPD of a private hospital in Karachi.

Methodology: 60 diagnosed patients of knee osteoarthritis were included in this study. Male and female patients ≥ 50 years of age, fulfilling the inclusion criteria and after written informed consent experienced a wash-out period of 72 hours. These patients were systematically randomized into 2 groups each having 30 members. Group A received capsule Diacerein 50mg + capsule Ginger 550 mg twice daily and group B received capsule Diacerein 50mg twice daily, for 12 weeks. Parameters checked at 0, 6 and 12 weeks were: Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, pain at rest and movement (Visual Analogue Scale). Comparison of the two groups was done by independent t-test.

Results: Among 60 patients; 20 (33.33 %) were males and 40 (66.66%) were females. 4 patients in group A and 4 in B, dropped out during the study. Comparison of group A with group B in WOMAC and pain (at rest and movement) scores showed insignificant difference at day 0 before prescription of the drugs. However comparison showed highly significant difference (P -value < 0.001) between the two groups in WOMAC, pain at rest and movement scores at the end of 6th and 12th weeks of intervention.

Conclusion: Diacerein-Ginger is clinically more efficacious for management of knee OA than Diacerein alone.

Keywords: knee, osteoarthritis, ginger, diacerein, WOMAC score, pain score

INTRODUCTION:

Osteoarthritis (OA) is an inflammatory, degenerative disease of joints and most commonly affected age is above 50 years¹. This disease affects hands and weight-bearing joints however knee joint OA is the most common amongst all. Globally 3.8% of people are affected from knee osteoarthritis as compared to 0.85% prevalence of hip osteoarthritis. In South East Asia prevalence of knee OA is 2.2% in males and 3.8% in females².

OA can be divided into 'age related OA' that is related to advanced age and 'premature OA' which can be associated with a strong risk factor³. The bone shows sclerotic changes, formation of osteophytes but synovitis is also eminent⁴.

Pro-inflammatory mediators found to be commonly involved in OA are interleukin-1 α (IL-1 α), IL-1 β , IL-15, IL-17, IL-18, prostaglandins, tumor necrosis factor- α (TNF- α), nitric oxide (NO), matrix metalloproteinases (MMPs) and C-reactive protein⁵. These all are elevated in OA cartilage, sub-chondral bone, synovial membrane and fluid, thus produce a synergistic effect on pathways leading to enhancement of inflammation and cartilage degradation⁶.

Examination of the joint may reveal swelling and tenderness, limitation in range of movements and crepitus⁷. X-ray shows decrease in joint space narrowing that is predictive of articular cartilage loss; bone density is often maintained in this disease. Severity on radiograph can be graded according to Kallgren Lawrence scale. According to this scale osteoarthritis is categorized into 5 levels, these are 0: None, 1: Doubtful, 2: Minimal, 3: Moderate, 4: Severe⁸. In early disease X-ray can be normal, diagnosis is done clinically using American College of Rheumatology criteria for knee OA^{9,10}.

Among treatment modalities of knee OA, pharmacological treatment is the main stay. NSAIDs are the most common drugs used for knee OA, but are associated with number of adverse effects¹¹. According to European Society for Clinical and Economic Aspects of Osteoarthritis (ESCEO) improvement and control of symptoms can be achieved by symptomatic slow-acting drugs for OA (SYSADOAs) including diacerein¹². It is an anthraquinone derivative, and its active metabolite is rhein. The key mechanism of action of diacerein is to inhibit the interleukin-1 β (IL-1 β) system

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and subsequent signaling. Diacerein not only has anti-inflammatory effect but also has some anti-catabolic and pro-anabolic effects on synovial membrane and cartilage. Moreover Diacerein has lesser adverse effects when compared with NSAIDs¹³.

Osteoarthritis Research Society International (OARSI) and some authors suggest more research, as efficacy of Diacerein as a single agent is still undecided¹⁴. Research has shown the trend of people suffering from osteoarthritis to use alternative medicine more than any other chronic disease¹⁵. These reasons compelled addition of a herbal agent that is ginger to the available agents for management of osteoarthritis. In this study ginger was chosen to be used with diacerein for knee OA as it is easily available and economical food spice in South East Asia.

Zingerber officinale is scientific name of ginger. Besides its use as a spice it is also a folk medicine in South East Asia. It is used for gingivitis, rheumatoid arthritis, cold, emesis and as expectorant. Active ingredients of ginger include shagoal, gingerol, paradol, zingerol and zerurnborne¹⁶. Underlying mechanism is cyclo-oxygenase inhibition resulting in prostaglandin synthesis inhibition but Lipoxygenase pathway is also inhibited by ginger. Nitrous oxide, protein C, IL-1 β , TNF- α levels are also found to be reduced. Ginger has also found to have chondroprotective role in OA¹⁷. As ginger has a proved anti-inflammatory effect; it can be used alone or in addition to present pharmacological options for effective symptomatic treatment of knee OA. This study was conducted to compare clinical efficacy of diacerein with ginger-diacerein alone in treating knee OA.

METHODOLOGY:

The study was conducted in medical OPD of a private hospital in Karachi from 21st September 2018 till 31st March 2019. Faculty Research Committee (FRC) and Ethical Review Committee (ERC) of Bahria University Medical and Dental College approved this study. After informed written consent 60 patients of knee OA were included in the study.

Inclusion criteria were; males and females ≥ 50 years of age suffering from knee osteoarthritis requiring regular medical treatment. Clinical and X-ray findings of the patients were according to the American College of Rheumatology criteria for knee osteoarthritis⁹ and radiographic evidence of knee OA in concordance with Kallgren-Lawrence grade of 1 to 3¹⁸. Patients having known history of hypersensitivity to the study drugs, Kallgren-Lawrence grade of 0 or 4, concurrent other inflammatory or traumatic joint disease, recent or concurrent major illness of hepatic, renal, cardiovascular, gastrointestinal, hematopoietic or endocrine systems, terminal illness or cancer, overweight defined as a BMI >30 , pregnancy or

lactation (women) and intra-articular or systemic corticosteroid therapy in 3 months preceding enrolment for the study were excluded from the study.

After fulfilling the inclusion criteria 60 patients were selected. Before giving any intervention these patients were given wash out period of 72 hours for any drug. The patients were divided through simple systematic randomization into two groups: Group A (n=30) were prescribed with capsule Diacerein 50 mg + capsule Ginger 550 mg orally twice daily for 12 weeks. Group B (n=30) patients were given with capsule Diacerein 50 mg orally twice daily for 12 weeks.

For recording demographic profile and study parameters a pre-designed evaluation form was used. Four patients in group A (n=26) and 4 patients in group B (n=26) dropped out during the study. Composite Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and Visual Analogue Scale (VAS) were used to compare the clinical efficacy of the two groups at beginning and end of 6th and 12th week of intervention. WOMAC index is a 24 item questionnaire and evaluates pain, stiffness and difficulty in physical activity in knee OA. Higher scores show worsening of the disease and a decline in the score is depictive of improvement. VAS was used to assess pain at rest and movement. A 10 cm scale numbered from 0 to 10 was used as VAS; 10 being the worst pain and 0 showing no pain. Hence decrease in VAS showed improvement. Statistical analysis was done using SPSS version 23.0. Normality of the data was assessed by plotting histogram. Independent t-test was applied to check difference between the two groups. P ≤ 0.05 was considered to be statistically significant.

RESULTS:

In this study out of 60 patients of knee OA; females were more (66.66%) than males (33.33%), as shown in table 1. In group A mean age was 57.70 \pm 4.37 and in group B was 57.69 \pm 4.55. Mean BMI of the patients in group A was 28.28 \pm 1.19 whereas 28.08 \pm 1.53 in group B.

Parameter wise comparison of the two groups (independent t-test) was conducted at the beginning of the study (Day 0) before giving any intervention and also at the end of 6th and 12th weeks of intervention. Table 2 demonstrates comparison of WOMAC scores of the two groups. At day 0 mean of WOMAC score of group A was 36.27 \pm 8.57 and group B was 36.20 \pm 8.07 showing no significant difference (P-value = 0.975). At the end of 6th week of intervention means of WOMAC score in group A and B patients were 20.04 \pm 5.95 and 32.85 \pm 7.78 (P-value < 0.001) showing more improvement in group A. WOMAC score's mean at the end of 12th week of intervention in group A (9.96 \pm 2.25) showed marked improvement than group B (29.62 \pm 7.03) with P-value< 0.001.

Means of pain at rest (measured by VAS) before intervention were 2.53 \pm 0.90 and 2.57 \pm 0.77 for group A and B respectively as demonstrated in table 3. After 6weeks of intervention

mean for group A was 1.37 ± 0.69 and group B was 2.12 ± 0.43 (P -value < 0.001). Pain at rest for group A (0.50 ± 0.51) and for group B (1.62 ± 0.57) showed highly significant difference at the end of 12th week (P -value < 0.001).

Comparison of pain at movement (VAS) between the two groups is shown in table 4. It is clearly shown that no

Table 1: Distribution of the Patients Included in the Study Suffering from knee Osteoarthritis

Groups	Total no. Of patients	Males	Females	Drop out
A	30	9	21	4
B	30	11	19	4
TOTAL	60	20 (33.33%)	40 (66.66%)	8

Table 2: Comparison of WOMAC scores of Diacerein + ginger (group A) and Diacerein alone (group B)

	Mean ± Standard Deviation		P-VALUE ^δ
	Group A	Group B	
Day 0	36.27±8.57	36.20±8.07	0.975*
6 th week	20.04±5.95	32.85±7.78	< 0.001**
12 th week	9.96 ± 2.25	29.62 ± 7.03	< 0.001**

^δindependent t-test

*insignificant P-value > 0.05

**highly significant P-value < 0.01

Table 3: Comparison of Pain at rest of Diacerein + ginger (group A) and Diacerein alone (group B)

	Mean ± Standard Deviation		P-VALUE ^δ
	Group A	Group B	
Day 0	2.53±0.90	2.57±0.77	0.878*
6 th week	1.37±0.69	2.12±0.43	< 0.001**
12 th week	0.50±0.51	1.62±0.57	< 0.001**

^δindependent t-test

*insignificant P-value > 0.05

**highly significant P-value < 0.01

Table 4 Comparison of Pain at movement of Diacerein + ginger (group A) and Diacerein alone (group B)

	Mean ± Standard Deviation		P-VALUE ^δ
	Group A	Group B	
Day 0	5.33±0.99	5.40±0.77	0.773*
6 th week	3.56±0.85	4.42±0.81	< 0.001**
12 th week	2.27 ± 0.45	3.38 ± 0.75	< 0.001**

^δindependent t-test

*insignificant P-value > 0.05

**highly significant P-value < 0.01

significant difference was there at day 0 between group A (5.33 ± 0.99) and group B (5.40 ± 0.77) with P -value = 0.773. However at the end of 6th and 12th weeks of intervention; marked difference between the groups was observed (P -value < 0.001).

DISCUSSION:

Primary OA is the most common type of arthritis especially at age more than 50 years. This has been shown in a study conducted in India where people having age more than 50 years had OA more than those having age between 40-45 years. In our study 69.8% of the participants were females as compared to 30.8% males. The Indian study showed similar results where prevalence of knee OA was more in females (31.6%) than males (28.1%)¹⁹. Another study conducted in Sri Lanka also showed knee OA prevalence to be 20.1% in female population above 50 years of age. Exact underlying cause of knee OA being more prevalent in females is still unknown²⁰.

In this study mean BMI of the participant was 28.18, hence most of the patients were overweight. This is in compatible with the Indian study in which prevalence of knee OA was found to be significantly high in overweight / obese as compared to under or normal weight patients. Moreover obesity is a known risk factor for knee OA¹⁹.

Limited studies are available regarding effect of ginger, alone or in combination with other pharmacological options, on knee OA especially with diacerein. In our study diacerein combination with ginger has produced highly significant difference (P -value < 0.001) in all parameters, as compared to diacerein alone.

Another study was conducted on 90 knee OA patients, with the objective to evaluate effect of ginger on pain of the patients. The patients were randomized to ginger and control groups for 12 weeks. The ginger group ($n=45$) was taking conventional osteoarthritis treatment prescribed by orthopedic specialist and 1000mg of ginger per day in two divided doses. The control group ($n=45$) was only taking the conventional treatment given by the orthopedic specialist. Pain of the patients was assessed using visual analogue score (VAS) at the beginning and end of the study. The pain scores declined in both groups but more in the ginger group (P -value = 0.001). Hence the results are in accord with our study²¹.

Another trial showing similar results was conducted in India on 60 patients of knee OA, which were randomly divided into 3 groups. Group I was given Tab. Diclofenac 50 mg and Cap. Placebo, group II received Cap. Ginger 750 mg and Cap. Placebo and group III was given Cap. Ginger 750 mg and Tab. Diclofenac 50 mg. The patients were assessed every 2 weeks till 12 weeks of study. A statistically significant improvement in WOMAC index and Visual Analogue Score was seen in group III (P -value < 0.001). Thus ginger powder had an add-on effect with NSAIDs in treating osteoarthritis²².

Another study was conducted on 120 patients of knee OA; it was a double blinded randomized trial. The participants were randomly divided into two groups; one group received capsule ginger 500mg per day and the other received capsule placebo (containing starch) for 12 weeks. Pain scores (noted on VAS) were significantly reduced in ginger group (P -value < 0.001), hence showing concordance with our study²³.

A meta-analysis was conducted by OARSI regarding efficacy and safety of ginger in osteoarthritis. 5 randomized placebo controlled trials were included in this meta-analysis.

Range of average age of participants was 47 to 66 years with more percentage of women. The daily dose of ginger ranged from 500mg to 1000mg per day and the trials duration ranged from 3 to 12 weeks. The analysis showed that ginger caused statistically significant decline in pain ($p=0.005$) and disability ($p=0.01$). The author concluded that ginger was efficacious and safe for reducing pain and inflammation of OA. The results of the meta-analysis are in agreement with our study showing improvement in ginger groups²⁴.

The present study and other mentioned studies demonstrated better symptomatic relief with ginger combinations, in patients with knee OA. Hence physicians should consider use of ginger in this regard. However long term and multicenter studies should be conducted with larger sample size; considering ginger alone group as well.

CONCLUSION:

Diacerein with ginger is clinically more effective in treating knee osteoarthritis as compare to diacerein alone.

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