

“A Comparative study to estimate the efficacy of Diacerein and Diclofenac given alone or in combination to Osteoarthritic population with respect to pain alleviation and regaining joint function”.

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Abstract:

Introduction: Osteoarthritis (OA) is a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins. OA is the most common joint disease of human both in the western world as well as India. Age, Major joint trauma and repetitive joint use (Anterior cruciate ligament insufficiency or meniscus damage and meniscectomy), Obesity, genetic differences have been found as risk factors for development of OA. Cardinal feature of OA is progressive loss of articular cartilage where all the components of synovial joint: subchondral bone, synovium, meniscus, ligaments and supporting neuromuscular apparatus as well as cartilage are affected. Remodeling and hypertrophy of bone are major features of OA. . Pharmacologic therapy includes topical and oral use of Non- steroidal anti- inflammatory drugs (NSAIDs), paracetamol, selective COX-2 inhibitors, opioids, intra-articular/ peri- articular glucocorticoids or hyaluronate injection. Dacetine, specifically its active diacetyl derivatives, rhein, is an interleukin-1 inhibitor. Rhein is an anthraquinone found in plants of the genus Cassia and has moderate anti-inflammatory and analgesic activity and weak laxative effects. There is a comparison on its analgesics efficacy and carry- over effect standard NSAID drug used in OA patients and to see the efficacy and safety of combining diclofenac given at reduced dose when compared to standard therapy.

Aims & Objective: To study the efficacy and adverse effect profile of Diacerein and Diclofenac given alone or in combination in Indian osteoarthritic population with respect to pain alleviation and regaining joint function also the carry-over effect of Diacerein and Diacerein-Diclofenac combination in comparison to Diclofenac given alone.

MATERIALS AND METHODS: The study was conducted in Department of Pharmacology and Department of Orthopaedics of Saraswathi Institute of Medical Sciences. During the period of September 2018 to January 2019. A single-blind, randomized, parallel, comparative model was designed for the study. Patients attending the OPD of Orthopedics Department, Saraswathi Hospital were screened for Osteoarthritis of knee.

RESULT: There is a carry over effect as suggested by the primary efficacy end point. Diacerein as well as the combination have a carry over effect which provides significant maintenance of pain and function when compared to diclofenac when the drugs are withdrawn. Pain during walking is decreased both by diacerein and combination at least as much as diclofenac. But if overall activity of subject is taken into account, diacerein is better than combination as well as diclofenac alone.

CONCLUSION: Diacerein has been studied in patient suffering from OA and its efficacy and safety compared to standard treatment regimens. Diacerein has been shown to be as efficacious as standard NSAIDs like diclofenac are in addition, has been shown to possess carry-over effect. This leads to less analgesic consumption after stopping diacerein. Meta analysis and systematic review of the studies done reveal that there is a small but significant benefit of diacerein over NSAIDs because of its analgesic action and carry-over effect.

Key words: Osteoarthritis (OA), NSAIDs

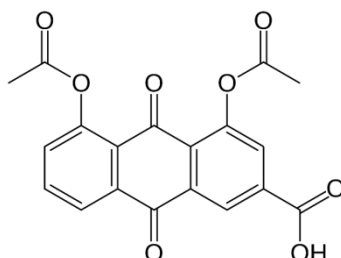
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I. Introduction

OA is the most common joint disease of human both in the western world as well as India. Age, Major joint trauma and repetitive joint use (Anterior cruciate ligament insufficiency or meniscus damage and meniscectomy), Obesity, genetic differences have been found as risk factors for development of OA. Cardinal feature of OA is progressive loss of articular cartilage where all the components of synovial joint: subchondral

bone, synovium, meniscus, ligaments and supporting neuromuscular apparatus as well as cartilage are affected are affected. Remodeling and hypertrophy of bone are major features of OA. Cartilage contains a family of matrix metalloproteinases (MMPs), including stromelysin, collagenase, and gelatinase, which can degrade all the components of extracellular matrix at neutral pH. The turnover of normal cartilage is affected through a degradation cascade; the driving force appears to be interleukin (IL)-1, a cytokine produced by mononuclear cells and synthesized by chondrocytes. In addition to its catabolic on cartilage, IL-1 suppresses PG synthesis by the chondrocyte, inhibiting matrix repair. Clinical trials on human volunteers for shorter duration (~1 month) have shown variable results when compared to standard NSAID therapy. Long term studies have shown that diacerein decreases the progression of OA and there is evidence of carry-over effect of the drug when the drug is discontinued with respect to pain relief and maintenance of joint.



Chemical structure of Diacerein

Diacerein is a drug for the treatment of patients with osteoarthritis. Diacerein, specifically its active diacetyl derivative, rhein, is an interleukin-1 inhibitor. Rhein is an anthraquinone found in plants of the genus *Cassia* and has moderate anti-inflammatory and analgesic activity and weak laxative effects. In animal and in vitro human experiments, reduced fibrinolytic activity in synovial fluid and synovial fibroblasts, inhibitions of superoxide anion production, lysosomal enzyme release and chemotaxis. There was improvement of OA induced in animal models when treated with diacerein. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin syntheses, diacerein stimulates or does not affect prostaglandin synthesis, with no prejudice to gastric mucosal or renal function.

II. Methodology

Study design: A single-blind, randomized, parallel, comparative model was designed for the study. Patients attending the OPD of Orthopedics Department, Saraswathi Hospital were screened for Osteoarthritis of knee. After meeting the inclusion and exclusion criteria and signing the informed consent form, patients were randomized into three groups who received diacerein or diclofenac or both diacerein and diclofenac respectively. All the groups also received Omeprazole 20mg in addition. Following 2 months of therapy, patients were followed up for another 1 month.

Study period: The present study was conducted during the period of September 2018 to January 2019.

Study population: A total of 189 subjects were screened. Seventy one subjects were excluded as they did not meet inclusion criteria or fell in the exclusion criteria. Twenty-two subjects did not give consent for enrolment in the study and 15 withdrew as they expressed their inability to come for regular follow-up every 2 weeks. Of the 81 subjects who entered the study, 4 subjects were excluded from the study as they were assessed to be uncooperative, non-motivated and/or negligent and were prone to discontinue from the study midway. The remaining 77 subjects completed the study with 26 subjects in diacerein group, 26 patients in diclofenac group and 25 patients in combination (Diacerein and Diclofenac) group. One subject in diacerein group suffered a serious adverse event and discontinued from the study after 4 weeks of treatment. Thus 76 subjects were finally included in the efficacy analysis. The Diacerein group, Diclofenac Group and the combination treated group have been named as Group 1, Group 2 and Group 3 respectively.

STATICAL ANALYSIS: The three groups were compared using ANOVA while intra-group comparison was done using paired test. The categorical values were compared using chi-square test. The software used for all statistical analysis was SPSS ver 10.0 and was done using

Table 1: Baseline Demography of study groups

	Diacerein	Diclofenac	Combination	P value
Age (years)	53.33±2.15	54.81±1.94	57.6±2.05	0.336
Male subjects	10	10	10	0.974
Female subjects	15	16	15	0.974
Weight (kg)	74.72±2.32	74.12±2.13	75.12±1.87	0.944
Height (cm)	163.66±18	162.96±15	163.8±18	0.932

Income (in Rs./mth)	7108.7±1368	5704.5±880.7	6886.4±1215	0.666
BMI (kg/m ²)	27.88±0.69	28.13±1.01	28.18±0.88	0.969

Numbers indicate value ± standard deviation. P value is obtained by comparing the three groups by ANOVA.

Table 2: WOMAC function sub score of the three groups

	Diacerin	S.D.	95% CI	Diclofenac	S.D.	95% CI	Combination	S.D.	95% CI	P value
Wk 0	102.928	17.359	95.76-110.09	104.323	10.923	99.91-108.73	104.328	14.212	98.46-110.19	0.924
Wk 4	88.92	20.32	80.53-97.31	92.11	13.04	86.84-97.38	89.64	16.47	82.85-96.44	0.777
Wk 8	72.644	19.579	64.56-80.72	79.231	15.192	73.09-85.36	73.144	17.135	66.07-80.21	0.324
Wk 12	57.632	16.461	50.83-64.42	70.888	15.523	64.61-77.15	62.52	16.756	55.60-69.43	0.016
Wk 16	52.448	13.484	46.88-58.01	73.708	15.074	67.61-79.79	61.96	16.101	55.31-68.60	<0.001

Thus, overall improvement in scores was significant in diacerein group at week 12 and 16 compared to diclofenac therapy

III. Discussion

The present randomized open label study was designed to confirm these findings in selected patients. Firstly, it is assessed if the drug indeed had analgesic efficacy similar to that of diclofenac, a commonly used NSAID in OA. Second research question was to find if adding diacerein to diclofenac decreases the requirement of each of them while providing adequate analgesia. Thirdly, we wanted to corroborate the carry over effects of diacerein and test whether the combination of diacerein and diclofenac also has an equivalent or greater carry over effect. Fourthly, we wanted to assess any significant change in the quality of life in patients of these treatment groups. Finally, we wanted to evaluate the adverse event profile of Diacerein and compare it to that of diclofenac. in the intent- to –treat population. 100mg/day diacerein (50mg twice daily) was significantly superior (P<0.05) to placebo using the primary criterion (visual analog scale [VAS] assessment of pain on movement). Significant improvement (P<0.05) was also observed for the secondary criteria, which included the Western Ontario and Mc Master Universities OA index (WOMAC), the WOMAC subs cores, and the VAS assessment of handicap. In patients treated with diacerein dosages of 50mg/ day and 150mg/day, favorable but not significant results were observed for the primary criterion. The best daily dosage of diacerein, calculated from the effect on the VAS assessment of pain on movement, was 90.1 mg in the per-protocol population, the analysis of the primary criterion showed significant dose- dependent differences (p <0.05) between each of the 3 diacerein dosages and the placebo. No differences were observed among the diacerein group. A significantly higher incidence (p< 0.05) of adverse events (AEs), as well as a higher rate of dropout due to AEs, was observed in patients treated with 150mg/ day diacerein versus those treated with placebo, 50mg/ day diacerein, or 100mg/ day diacerein. Mild-to-moderate transient changes in bowel habits were the most frequent AEs, increasing with the dosage. The authors concluded that Diacerein, was an and safety, the optimal dai8ly dosage of diacerein for patients with knee OA was found to be 100 mg/day (50mg twice daily).

IV. Conclusion

Patients suffering from OA at an early age must be counseled regarding the disease along with all the treatment modalities available. They must also be counseled regarding the value of exercise and physiotherapy. Pain during walking is decreased both by diacerein and combination at least as much as diclofenac. But if overall activity of subject is taken into account, diacerein is better than combination as well as diclofenac alone. There is a carry over effect as suggested by the primary efficacy end point. Diacerein as well as the combination have a carry over effect which provides significant maintenance of pain and function when compared to diclofenac when the drugs are withdrawn.

Diacerein users required less PCM as rescue medication than diclofenac users at week 12. It is also evident that once the drugs are stopped, diacerein users (alone or in combination with diclofenac) require less PCM than diclofenac users

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