

RESEARCH

A RANDOMIZED, ACTIVE CONTROLLED, CLINICAL TRIAL TO ASSESS THE EFFICACY AND SAFETY OF CELECOXIB + DIACEREIN FIXED DOSE COMBINATION IN ADULT INDIAN PATIENTS SUFFERING FROM OSTEOARTHRITIS

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ABSTRACT

Background: Osteoarthritis of knee and/or hip joints is a common disorder associated with a significant morbidity in the elderly patients. Celecoxib + Diacerein Fixed Dose Combination (FDC) can be a useful medication for the treatment of osteoarthritis of knee and/or hip joints. **Objective:** To compare efficacy and safety of Celecoxib + Diacerein FDC capsules given twice daily with Aceclofenac + Diacerein FDC tablets given twice daily in the management of osteoarthritis of knee and/or hip joints in adult Indian patients. **Methods:** Clinically symptomatic patients with osteoarthritis of knee and/or hip joints were randomized to treatment with Celecoxib 100 mg + Diacerein 50 mg FDC capsules or Aceclofenac 100 mg + Diacerein 50 mg FDC tablets each given twice daily for 4 weeks in this comparative clinical trial. Efficacy assessments were carried out using pre-validated SAS (Short Arthritis Assessment Scale) questionnaire. **Results:** Celecoxib + Diacerein FDC capsules (n=12) produced significant improvement in Pain, Physical Function & Overall well-being aspects of SAS questionnaire at the end of treatment period as compared to baseline (p<0.05 for all). Similar results were obtained with Aceclofenac + Diacerein FDC tablets (n=13); there was no statistically significant difference between the two treatment groups. Celecoxib + Diacerein FDC capsules were excellently tolerated and none of the patients enrolled in either of the groups reported any adverse event. **Conclusion:** Celecoxib + Diacerein FDC capsules are equally efficacious as Aceclofenac + Diacerein FDC tablets and excellently tolerated for the treatment of osteoarthritis of knee and/or hip joints in adult Indian patients.

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INTRODUCTION

Osteoarthritis of knee and/or hip joints is a common disorder associated with a significant morbidity in the elderly patients.[1] Celecoxib is a Non-Steroidal Anti-Inflammatory Drug (NSAID) which is a selective inhibitor of cyclo-oxygenase 2 (COX-2). While, COX-2 is an inducible enzyme that generates inflammatory prostaglandins at sites of inflammation, COX-1 enhances mucosal perfusion, bicarbonate production and mucus production - key gastric defense mechanisms. Selective COX-2 inhibitors like Celecoxib, therefore reduce pain and inflammation without gastrointestinal side effects. Celecoxib capsules are already approved internationally for the treatment of osteoarthritis for the past several years.[2] On the other hand, Diacerein is classified as a Structural modifying anti-osteoarthritic drug (SMOAD) or Disease modifying anti-osteoarthritic drug (DMOAD) that has been developed specifically for the treatment of osteoarthritis. It has a novel mode of action that differentiates it from NSAIDs. Diacerein inhibits the

production of interleukin-1 beta by human monocytes and the effects of the cytokine on chondrocytes, thus exerting chondroprotective effects on articular cartilage and reducing severity of cartilage, bone, and synovial membrane damage in osteoarthritis. There appears to be some inhibitory effects on leucocyte migration and activation, contributing to the weak anti-inflammatory activity. Diacerein does not block the synthesis of prostaglandins but may actually stimulate its synthesis, especially PGF-2 alpha, a prostaglandin with cytoprotective effect on the gastric mucosa.[3, 4]

Since, both Celecoxib and Diacerein are useful in the treatment of osteoarthritis and have a distinct mechanism of action; it would therefore be justifiable to combine both these drugs for their synergistic activity in the treatment of osteoarthritis. Further, there is no reported pharmacokinetic or pharmacodynamic interaction between Celecoxib and Diacerein and the safety

and efficacy of both these individual drugs is already well-established. In fact, Diacerein is frequently used concomitantly with NSAIDs and its fixed dose combination with this class of drug, Aceclofenac, is also available for the treatment of osteoarthritis in our country as of date.

The present study was conducted to demonstrate efficacy and safety of Celecoxib 100 mg + Diacerein 50 mg Fixed Dose Combination (FDC) capsules given twice daily in adult Indian patients suffering from osteoarthritis of knee and/or hip joints in comparison with Aceclofenac 100 mg + Diacerein 50 mg FDC tablets given twice daily.

MATERIALS AND METHODS

Patients

Patients of either sex aged 18-60 years, and with an established diagnosis of osteoarthritis of knee and/or hip joints with at least moderate pain [at least 5 on the Visual Analogue Scale of 0 to 10 cm in Short Arthritis Assessment Scale (0 being no pain and 10 being severe pain)] at the affected site were screened for the study after taking their informed consent.

Patients with hypersensitivity to Celecoxib, Aceclofenac, any other NSAIDs, Diacerein, anthraquinone derivatives or sulfonamides were excluded from the study. Patients with hepatic or renal insufficiency, active peptic ulceration within the last 6 months, those suffering from coronary heart disease, any other significant cardiovascular disorder or hemorrhagic diathesis were also not included. Patients with bronchial asthma, rhinitis, urticaria, or other allergic reactions induced by aspirin or other NSAIDs, continuing history of alcohol and / or drug abuse and those who have participated in another clinical trial in the past 3 months were excluded from the study. Pregnant and lactating women and persons suffering from clinically significant uncontrolled disease of any body system were also not included in the study.

Patients were not permitted to take any analgesics (NSAIDs or non-NSAIDs), muscle relaxants (both systemic or topical), glucocorticoids or benzodiazepines concomitantly along with the study medication. Concomitant administration of Lithium, Fluconazole and oral anticoagulants was not permitted during the entire study period to avoid adverse drug interactions. Paracetamol 500 mg tablets were permitted as a rescue medication and a record of their usage was maintained for each patient. Routine prophylactic use of gastro-protective agents like proton pump inhibitors, H₂ receptor blockers, antacids etc. was also not permissible during the entire course of the study. However, if indicated clinically during the course of the study in the best interest of the patient, a record of their usage was maintained. All other concomitant medications for concomitant illnesses not known to interact with study medications which could be used as deemed necessary by the investigator were recorded.

Procedures

This randomized, active controlled, comparative clinical trial was approved by the Drugs Controller General of India (DCGI) and institutional ethics committee of the institute.

Efficacy assessments were carried out using a validated questionnaire; Short Arthritis Assessment Scale – SAS,[5] that was explained to the patients at the time of entry into the study. Assessment of SAS included measurement of pain, physical functionality and overall

well-being on a Visual Analogue Scale (VAS) of 0 to 10 cm. Patients were randomly allocated to receive either Celecoxib 100 mg + Diacerein 50 mg FDC capsules twice daily or Aceclofenac 100 mg + Diacerein 50 mg FDC tablets twice daily for the entire duration of the study i.e., 4 weeks. Patients were followed up on an outpatient basis with a weekly schedule of visits. Hematological and biochemical investigations like complete haemogram, liver and renal function tests were done at the screening visit and at the end of treatment. Clinical adverse events, if any, were recorded on each of the visits along with their nature, intensity, action taken, relationship to the study drug and outcome.

All efficacy and safety assessments were carried out on the intent-to-treat population, which comprised all the enrolled patients who received at least 7 days' treatment and provided at least one post-baseline efficacy or safety data. The primary efficacy end point was the degree of improvement in the Pain aspect of SAS questionnaire on VAS at the end of therapy (i.e. Week 4) and at each follow-up visit as compared to baseline (i.e. Week 0). Secondary efficacy end points were the degree of improvement in the Physical function & Overall well-being aspects of SAS questionnaire on VAS at the end of therapy (i.e. Week 4) and at each follow-up visit as compared to baseline (i.e. Week 0) and the investigators' global assessment of efficacy at the end of the study. Data are presented as mean ± SD (range) or number & % of appropriate populations. Statistical analysis was carried out using two-tailed paired t-test, unpaired t-test assuming unequal variance and chi-square test according to the data characteristics. P values less than 0.05 were considered to be statistically significant.

RESULTS

As per the inclusion and exclusion criteria of the Protocol, a total of 25 patients were enrolled in this study. Of these, 12 patients were enrolled in Group 1 (Celecoxib + Diacerein FDC capsules) and 13 patients were enrolled in Group 2 (Aceclofenac + Diacerein FDC tablets). All the 25 patients in Group 1 and Group 2 completed the study as per the Protocol. Therefore, all these 25 patients were considered for efficacy and tolerability analysis at the end of the study i.e., Week 4. The detailed demographic profile of the patients enrolled in both the groups is depicted in Table I.

Table I: Demographic profile

Group	Group 1 (n=12)	Group 2 (n=13)
Age (yrs)	47.4 ± 7.4 (40-60)	52.2 ± 7.0 (40-60)
Weight (kg)	62.0 ± 9.2 (48-74)	68.0 ± 5.1 (62-80)
Height (cm)	149.9 ± 14.9 (120-172)	159.2 ± 7.8 (150-175)
Duration of illness (months)	6.0 ± 5.8 (3-24)	5.2 ± 3.2 (2-12)
Sex	Male	3 (25.0%)
	Female	9 (75.0%)
		4 (30.8%)
		9 (69.2%)

Efficacy assessments

The primary efficacy variable was the degree of improvement in the pain aspect of SAS questionnaire on VAS at the end of therapy i.e., Week 4 and at each follow-up visit as compared to baseline i.e., Week 0. As depicted in Table II, the mean score declined significantly at each visit from 5.8 ± 0.8 (range: 4-7) at baseline to 1.9 ± 0.7 (range: 1-3) at Week 4 in Group 1 (p<0.05) and from 6.4 ± 0.8 (range: 5-8) at baseline to 2.3 ± 0.6 (range: 1-3) at Week 4 in Group

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2 ($p < 0.05$). The improvements were not statistically ($p > 0.05$) significantly different between the two treatment groups

Table II: Change in the mean score of primary efficacy variable on SAS questionnaire as assessed on a weekly basis

Parameter	Group	Visit 1 (Week 0)	Visit 2 (Week 1)	Visit 3 (Week 2)	Visit 4 (Week 3)	Visit 5 (Week 4)
Mean Pain score	Group 1 (n=12)	5.8 ± 0.8 (4-7)	4.5 ± 0.9 (3-6)	3.6 ± 0.8 (3-5)	2.8 ± 0.7 (2-4)	1.9 ± 0.7 (1-3)
	Group 2 (n=13)	6.4 ± 0.8 (5-8)	4.8 ± 1.1 (3-6)	3.8 ± 0.8 (3-5)	3.1 ± 0.3 (3-4)	2.3 ± 0.6 (1-3)

In the degree of improvement in the Physical function aspect of SAS questionnaire on VAS at the end of therapy (i.e. Week 4) and at each follow-up visit as compared to baseline (i.e. Week 0); the mean scores for the difficulty felt by the patients while going downstairs & going for shopping declined significantly at each visit as compared to baseline as depicted in Table III. For each of the parameter in each of the treatment group, a significant improvement was noted at the end of treatment period as compared to baseline ($p < 0.05$ for all); while response was similar between the two groups ($p > 0.05$).

Table III: Change in the mean score of physical function aspect of SAS questionnaire as assessed on a weekly basis

Parameter	Group	Visit 1 (Week 0)	Visit 2 (Week 1)	Visit 3 (Week 2)	Visit 4 (Week 3)	Visit 5 (Week 4)
Difficulty in going downstairs	Group 1 (n=12)	5.7 ± 0.8 (5-7)	4.5 ± 0.9 (3-6)	3.8 ± 0.8 (3-5)	3.2 ± 0.7 (2-5)	2.1 ± 0.7 (1-3)
	Group 2 (n=13)	6.0 ± 0.6 (5-7)	4.5 ± 1.1 (3-6)	3.8 ± 0.8 (3-5)	3.1 ± 0.6 (2-4)	2.5 ± 0.7 (1-3)
Difficulty in going for shopping	Group 1 (n=12)	5.8 ± 1.1 (4-7)	4.4 ± 1.2 (3-6)	3.8 ± 1.1 (3-6)	2.9 ± 0.5 (2-4)	2.3 ± 0.7 (1-3)
	Group 2 (n=13)	5.9 ± 0.9 (5-7)	4.7 ± 1.2 (3-6)	3.8 ± 0.8 (3-5)	3.2 ± 0.6 (2-4)	2.5 ± 0.7 (1-3)

In the degree of improvement in the overall well-being aspect of SAS questionnaire on VAS at the end of therapy (i.e. Week 4) and at each follow-up visit as compared to baseline (i.e. Week 0); as shown in Table IV, the mean score declined significantly at each visit as compared to baseline in Group 1 as well as Group 2 ($p < 0.05$ for both). The response however did not differ significantly on comparison of the two treatment groups ($p > 0.05$).

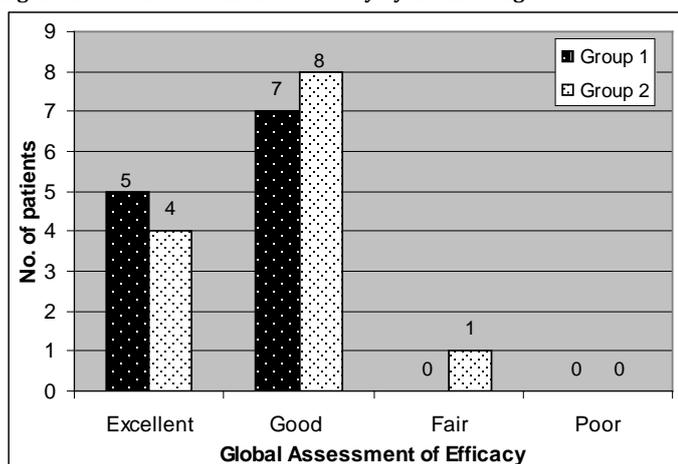
Table IV: Change in the mean score of overall well-being aspect of SAS questionnaire as assessed on a weekly basis

Parameter	Group	Visit 1 (Week 0)	Visit 2 (Week 1)	Visit 3 (Week 2)	Visit 4 (Week 3)	Visit 5 (Week 4)
Overall well-being	Group 1 (n=12)	5.5 ± 0.7 (5-7)	4.5 ± 1.1 (3-6)	3.8 ± 1.0 (3-6)	3.2 ± 0.7 (2-5)	2.3 ± 0.6 (1-3)
	Group 2 (n=13)	5.7 ± 0.8 (5-7)	4.5 ± 1.1 (3-6)	3.7 ± 0.6 (3-5)	3.1 ± 0.5 (2-4)	2.5 ± 0.7 (1-3)

The investigator ranked the global efficacy of the medication on a four-point rating scale at the end of study i.e., Week 4. All the 12 patients (100%) in Group 1 were rated to have either an “excellent” or a “good” efficacy to the study medication. On the other hand, 12 of the 13 patients (92.3%) in Group B were rated to have either an “excellent” or a “good” efficacy to the study medication at the end of the study.

The remaining 1 patient (7.7%) in Group B was rated to have a “fair” efficacy to the study medication at the end of the study ($p > 0.05$). The global assessment of efficacy given to the study medication at the end of the study is shown in Figure 1.

Figure 1: Global assessment of efficacy by the investigator



Group 1= Celecoxib + Diacerein FDC capsules (n=12), Group 2 = Aceclofenac + Diacerein FDC tablets (n=13), $p > 0.05$

Safety assessments

None of the patients discontinued the study due to adverse events or reported any adverse event in Group 1 or Group 2 during the entire course of the study. In addition, there was also no clinically significant change in any of the routine haematological and biochemical parameters as carried out at baseline and at the end of therapy with the study medication in any of the patients in both the groups. All the 25 patients including 12 patients in Group 1 and 13 patients in Group 2 were rated to have an “excellent” tolerability to the respective study medication on a four-point rating scale at the end of study i.e., Week 4.

DISCUSSION

The present study was carried out to assess the comparative efficacy and safety of Celecoxib + Diacerein FDC capsules and Aceclofenac + Diacerein FDC tablets, for the treatment of osteoarthritis of knee and/or hip joints in adult Indian patients. The results indicate that for the management of osteoarthritis of knee and/or hip joints,

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Celecoxib + Diacerein FDC capsules are as efficacious and well tolerated as Aceclofenac + Diacerein FDC tablets.

Efficacy and safety of Celecoxib and Diacerein both are well established for the treatment of osteoarthritis.[2-4] NSAIDs and disease modifying agents like Diacerein are frequently used concomitantly for the management of patients with osteoarthritis and a fixed dose combination of both these classes of drugs can be a suitable and convenient treatment modality. Osteoarthritis is a geriatric illness and patients of this age group generally have poor treatment compliance due to difficulty in memorising as well as in the intake of multiple medication doses.[6] FDC products can improve compliance to treatment in these patients. Thus, Celecoxib + Diacerein FDC capsules can offer comprehensive pain relief and prevent disease progression with good compliance to therapy.

The results of our clinical trial clearly suggest that Celecoxib + Diacerein FDC capsules provide significant pain relief with the therapy beginning as early as after one week of treatment. Physical functionality in carrying out day to day activities is also consistently improved during the 4 weeks of therapy. Both of these measures lead to improved overall well-being of the patients as well. According to the investigator's global assessment at the end of study also all the patients were rated to have "excellent" or "good" efficacy with the medication. Celecoxib + Diacerein FDC capsules were found to be equally efficacious as the active control group i.e. Aceclofenac + Diacerein FDC tablets; with no significant difference in any of the efficacy parameter.

The degree of pain reduction noted in our study with Celecoxib + Diacerein FDC capsules is consistent with the same reported in similar studies with NSAID and Diacerein combination therapy. Nguyen et al have reported degree of pain reduction with Tenoxicam & Diacerein combination therapy from 6.4 ± 1.2 at baseline to 3.2 ± 2.0 at the end of therapy;[7] while Singh et al have reported the reduction to 1.5 ± 0.5 at the end of treatment with Diclofenac & Diacerein combination as assessed on similar VAS.[8] A similar extent of pain relief is also noted in our study in Indian patients suffering from osteoarthritis of knee and/or hip joints receiving Celecoxib + Diacerein FDC capsules.

Limitations

This study demonstrates the efficacy and safety of Celecoxib + Diacerein FDC capsules in Indian patients. The open label design of the study is likely to be affected by the observer bias, which is inherent to all open label studies. However, trial design incorporating use of an active comparator that is current standard of care and use of validated efficacy assessment instruments as key primary and secondary efficacy variables ensure robustness of the

results of study. Further, disease modifying effects of Diacerein are difficult to judge from the short duration of the treatment and may become more apparent with continued therapy for longer duration, which can be assessed in future studies.

CONCLUSION

The results of this clinical trial demonstrate that Celecoxib + Diacerein FDC capsules are equally efficacious as Aceclofenac + Diacerein FDC tablets and excellently tolerated in adult patients suffering from osteoarthritis of knee and/or hip joints. Based on these findings Celecoxib + Diacerein FDC capsules can present suitable treatment option for the treatment of osteoarthritis of knee and/or hip joints in Indian patients.

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REFERENCES

1. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. (2011) The epidemiology of osteoarthritis in Asia. *Int J Rheum Dis.* 14:113-121.
2. McCormack PL. (2011) Celecoxib: a review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. *Drugs.* 71:2457-2489.
3. Medhi B, Singh PK, Prakash A, Sen R, Wadhwa S. (2007) Diacerein: A New Disease Modulating Agent in Osteoarthritis. *Indian Journal of Physical Medicine and Rehabilitation.* 18:48-52.
4. Rintelen B, Neumann K, Leeb BF. (2006) A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med.* 166:1899-1906.
5. Wolfe F, Michaud K, Kahler K, Omar M. (2004) The Short Arthritis Assessment Scale: a brief assessment questionnaire for rapid evaluation of arthritis severity in research and clinical practice. *J Rheumatol.* 31:2472-2479.
6. Hughes CM. (2004) Medication non-adherence in the elderly: how big is the problem? *Drugs Aging.* 21:793-811.
7. Nguyen M, Dougados M, Berdah L, Amor B. (1994) Diacerein in the treatment of osteoarthritis of the hip. *Arthritis Rheum.* 37:529-536.
8. Singh K, Sharma R, Rai J. (2012) Diacerein as adjuvant to diclofenac sodium in osteoarthritis knee. *Int J Rheum Dis.* 15:69-77.