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A Comparative Prospective Observational Study On The Efficacy And Safety Of Diacerein, Diclofenac, And Their Combination In The Management Of Osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is a chronic joint disease requiring long-term treatment that is both effective and safe. Diclofenac, a strong NSAID, provides quick symptomatic relief but comes with high GI and cardiovascular risks. Diacerein, an interleukin-1β inhibitor, gives delayed but long-standing relief from symptoms with a possible disease-modifying action. This research compared the clinical efficacy and safety of Diacerein monotherapy, Diclofenac monotherapy, and their combination in OA patients.

Methods: A six-month prospective, observational study was performed within the inpatient orthopedics unit of a tertiary care center. 109 patients with OA were recruited and divided into three groups: Diacerein (n=36), Diclofenac (n=36), and Combination therapy (n=37). The primary outcomes were the changes in inflammatory markers (Erythrocyte Sedimentation Rate - ESR, C-Reactive Protein - CRP) and pain severity (Visual Analog Scale - VAS). Secondary endpoints were improvement in function (Activities of Daily Living - ADL scale) and the frequency of adverse drug reactions (ADRs).

Results: All treatment groups had a statistically significant decline in ESR, CRP, and pain scores ($p<0.001$). The combination therapy group had the largest improvement: ESR decreased from 26.49 to 15.08, CRP decreased from 15.41 to 4.82, and pain scores decreased from 5.11 to 1.57. Only the combination group had a statistically significant increase in ADL scores ($p<0.001$). Safety analysis indicated that the combination group experienced the highest proportion of patients (72.9%) showing no adverse effects compared to Diclofenac monotherapy (52.8%) and Diacerein monotherapy (50%). A higher rate of stomach ulcers was reported for Diclofenac (25%).

Conclusion: The combination of Diacerein and Diclofenac much more effective than either drug alone in the prevention of inflammation, pain relief, and improvement in functional ability in osteoarthritis and with a better safety profile. Such synergy offers a rational basis for optimizing OA treatment by capitalizing on the fast onset action of an NSAID with the sustained action of a disease-modifying drug.

KEYWORDS: Osteoarthritis, Diacerein, Diclofenac, Combination Therapy, Anthraquinones, NSAIDs, Inflammation, Pain Management.

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1. INTRODUCTION

OA is one of the most frequent chronic degenerative joint diseases and a leading cause of disability throughout the world, characterized by progressive loss of cartilage, subchondral bone remodeling, and synovial inflammation [1]. The three major clinical features are pain, stiffness, and functional impairment, which severely diminish the quality of life [2]. Pharmacologic therapy is mainly for symptomatic relief, and Non-Steroidal Anti-Inflammatory Drugs like Diclofenac are the first choice for their potent anti-inflammatory and analgesic effect [3]. Prolonged use is limited for well-documented gastrointestinal, renal, and cardiovascular side effects. [4].

Diacerein, a derivative of anthraquinone, has a different mode of action. It is more of an interleukin-1β (IL-1β) inhibitor with modulation of the inflammatory cascade of cartilage degradation with potential disease-modifying properties [5]. It is slower in its action (2-4 weeks) but has a better GI safety profile compared with traditional NSAIDs [6].With their synergistic modes of action—Diacerein for long-term modulation of disease processes and Diclofenac for rapid symptomatic relief—a combination therapy promises enhanced efficacy with a reduced burden of side effects by allowing lower doses of Diclofenac. This study attempted to validate the hypothesis by comparing the clinical response and safety of Diacerein monotherapy, Diclofenac monotherapy, and their combination in real-life inpatient practice.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

A six-month prospective, observational study was conducted in the Department of Orthopedics of a government tertiary care hospital after clearance from the Institutional Ethics Committee (IEC Approval No: ECR/288/Ind t/TN/2018/RR-21/117).

2.2 Sample Population and Size

Sample size of 109 participants was determined through the use of the Raosoft ® online calculator with a confidence level of 95% and a margin of error of 5%, assuming a population of 150. 109 patients with OA diagnosis and on study medication were enrolled after signed informed consent.

2.3 Inclusion and Exclusion Criteria Inclusion criteria:

Patients aged ≥18 years who were diagnosed with OA and prescribed either Diacerein (50 mg BD), Diclofenac (50 mg BD), or both. Exclusion: Patients with a pre-existing hypersensitivity to the trial medication, pregnant or lactating women, unconscious patients, and patients with end-stage hepatic or renal failure.

2.4 Study Groups

The patients were classified into three groups based on the therapy type prescribed:

· Group A (n=36): Diacerein monotherapy (50 mg BD)
· Group B (n=36): Diclofenac monotherapy (50 mg BD)
· Group C (n=37): Combination therapy (Diacerein 50 mg BD + Diclofenac 50 mg BD)

2.5 Outcome Measures

· Primary Outcomes:
  · Inflammatory marker differences, e.g., ESR (mm/hr) and CRP (mg/L).
  · Difference in the severity of pain as perceived through the Visual Analog Scale (VAS; 0-10).
· Secondary Outcomes:
  · Change in functional status on Activities of Daily Living (ADL) scale.
  · Adverse Drug Reactions (ADRs) frequency and nature.

2.6 Statistical Analysis and Data Collection

The demographic, clinical variables, and outcome data were captured on a proforma at baseline and after the duration of treatment. SPSS version 27.0 was used for statistical analysis. Descriptive statistics were reported as mean ± standard deviation (SD) and frequencies (%). Inferential statistics included the Paired sample t-test to compare pre- and post-treatment values across groups, Chi-square test for investigating categorical ADR data, and ANOVA for comparing between groups. A p-value of <0.05 was considered statistically significant.

3. RESULTS

3.1 Baseline Characteristics:

The age of the study population was 57.4 years on average, with most (53.2%) falling within the 51- 60 year bracket. Baseline weight, height, and BMI were comparable across the three groups ($p>0.05$). A statistically significant difference in mean age between groups was noted ($p=0.029$) with the combination group being slightly older (60.7 ± 5.7 years). There were no significant differences in baseline ESR, CRP, VAS, and ADL scores, with a guarantee of comparability for outcomes analysis.

3.2 Efficacy Outcomes

Inflammatory Markers (ESR and CRP): A paired t-test showed statistically significant decrease($p<0.001$) in both ESR and CRP across all three groups post-treatment (Table 1).

· The most marked decrease was noticed in the Combination therapy group (ESR: 26.49 to 15.08; CRP: 15.41 to 4.82).

· The Diacerein group demonstrated a moderate decrease (ESR: 28.00 to 22.13; CRP: 14.41 to 11.00).

· The Diclofenac group was also improved profoundly (ESR: 23.24 to 17.78; CRP: 16.08 to 9.90).

Table 1: Changes in Inflammatory Markers (Paired t-test)

Group	Parameter	Pre-Treatment Mean	Post-Treatment Mean	p-value
Diacerein (n=36)	ESR	28.00	22.13	<0.001
	CRP	14.41	11.00	<0.001
Diclofenac (n=36)	ESR	23.24	17.78	<0.001
	CRP	16.08	9.90	<0.001
Combination (n=37)	ESR	26.49	15.08	<0.001
	CRP	15.41	4.82	<0.001

Pain and Functional Status: All groups reported a significant reduction in pain (VAS scores, $p<0.001$). The combination therapy again demonstrated superior analgesia (VAS: 5.11 to 1.57) compared to Diclofenac (5.39 to 3.36) and Diacerein (5.11 to 4.39) alone. Functional status, measured by the ADL scale, showed a statistically significant improvement only in the combination group ($p<0.001$), indicating that the reduction in pain and inflammation translated into better daily functionality.

3.3 Safety and Tolerability Adverse effects were monitored and recorded (Table 2). A Chi-square test showed a significant association between the treatment group and the incidence of ADRs ($\chi^2=27.043$, $p<0.001$).

· The Combination group had the highest proportion of patients (27/37, 72.9%) reporting no adverse effects.

· The Diclofenac monotherapy group reported the highest incidence of stomach ulcers (9/36, 25%).

· The Diacerein monotherapy group was associated with side effects like nausea (16.7%) and harmless urine discoloration (11.1%).

Table 2: Frequency of Adverse Drug Reactions

Adverse Effect	Diacerein (n=36)	Diclofenac (n=36)	Combination (n=37)	Total (n=109)
Nausea	6 (16.7%)	4 (11.1%)	4 (10.8%)	14 (12.8%)
Slight Urine Discoloration	4 (11.1%)	0 (0.0%)	0 (0.0%)	4 (3.7%)
Stomach Pain	8 (22.2%)	3 (8.3%)	3 (8.1%)	14 (12.8%)
Stomach Ulcer	0 (0.0%)	9 (25.0%)	3 (8.1%)	12 (11.0%)
Vomiting	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (0.9%)
No Adverse Effects	18 (50.0%)	19 (52.8%)	27 (73.0%)	64 (58.7%)

Paired Sample T test for comparing ESR and CRP levels for before and after treatment:

Table6.10:- Paired T test of ESR and CRP

Group	Mean ESR Before	Mean ESR After	p-value ESR	Mean CRP Before	Mean CRP After	p-value CRP
Diacerein	28.003	22.125	<0.001	14.406	11.000	<0.001
Diclofenac	23.236	17.775	<0.001	16.078	9.897	<0.001
Diacerein + Diclofenac	26.489	15.076	<0.001	15.405	4.819	<0.001

Paired sample t-test showed a statistically significant reduction in both ESR and CRP levels after treatment in all three study groups ($p<0.001$).

→ In Diacerein group, mean ESR reduced from 28.003 to 22.125 and CRP reduced from 14.406 to 11.000.
→ In Diclofenac group, mean ESR reduced from 23.236 to 17.775 and CRP reduced from 16.078 to 9.897.
→ In Combination group (Diacerein + Diclofenac), ESR reduced from 26.489 to 15.076 and CRP reduced from 15.405 to 4.819.

Maximum reduction in ESR and CRP was observed in the combination therapy group, indicating better anti-inflammatory efficacy compared to monotherapy groups.

Paired Sample T Test for ADL scale and Pain scale before and after treatment:

Table6.11:-Paired T test of Pain scale and ADL scale

Group	Mean Pain Scale Before	Mean Pain Scale After	p-value Pain	Mean ADL Scale Before	Mean ADL Scale After	p-value ADL
Diacerein	5.11	4.39	<0.001	5.19	5.42	**0.727**
Diclofenac	5.39	3.36	<0.001	5.19	5.58	**0.433**
Diacerein + Diclofenac	5.11	1.57	<0.001	4.89	5.59	**<0.001**

Paired sample t-test showed a statistically significant reduction in pain scale scores after treatment in all three study groups ($p<0.001$). The maximum reduction in pain score was observed in the combination therapy group, followed by Diclofenac group and Diacerein group respectively.
The ADL scale improvement (increase in score) after treatment was not statistically significant in Diacerein and Diclofenac groups

($p>0.05$), but significant improvement was observed in the combination therapy group ($p<0.001$), indicating better improvement in daily activity levels.

4. DISCUSSION

This study provides strong evidence for the superior efficacy and enhanced safety of Diacerein plus Diclofenac over single-agent approaches to the treatment of osteoarthritis. The findings are in accord with the pharmacologic rationale for combining the agents:

Diclofenac has short-term cyclooxygenase (COX) inhibition and prostaglandin-induced analgesia [7], while Diacerein has long-term regulation through inhibition of the IL-1β induced inflammatory cascade and cartilage degradation [5].

The maximum reduction in inflammatory biomarkers (ESR and CRP) was observed in the combination group. This is a sign of a synergistic anti-inflammatory effect, where Diclofenac's early suppression of acute inflammation is complemented and prolonged by Diacerein's effect on upstream cytokines, preventing rebound inflammation.

The increase in pain relief and more significantly, the significant increase in functional capacity (ADL scores) only in the combination group reflect a very significant clinical benefit. It indicates that the therapy not only reduces pain but also renders patients more functional in daily activities, which is a key goal in OA treatment.

The safety profile of the combination was excellent in relation to expectation. Contrary to the hypothesis that two drugs would contribute to side effects, the combination group experienced fewer ADRs. This could be because of the smaller required exposure to the peak toxic effects of Diclofenac due to the supportive anti-inflammatory action of Diacerein, or as a protective phenomenon. This is clinically important since GI complications are an important drawback of long-term NSAID administration [4].

Limitations: As an observational study, it is susceptible to selection bias. Treatment was for the length of inpatient stay only, and longer-term disease modification outcomes could not be assessed. A definitive validation would be a blinded, randomized controlled trial with long-term follow-up.

5. CONCLUSION

The combination of Diacerein and Diclofenac is an optimized treatment regimen for osteoarthritis. It synergistically offers rapid and efficacious anti-inflammatory and analgesic action and markedly enhances patients' functional status. Above all, it does this with a superior safety profile over Diclofenac monotherapy, avoiding the threat of severe GI side effects such as ulcers. This research recommends the sensible use of this combination therapy in the clinic for patients needing effective symptom control and enhanced mobility with reduced risk of complications. Long-term outcomes and potential for disease modification with combination regimens should be the targets of future research.

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