Clinical Study

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Efficacy, Disease-Modifying Effect and Safety of Arthrella Tablets v/s Diclofenac in the Management of Rheumatoid Arthritis: A Randomized, Comparative, Double Blind Study

Abstract

Rheumatoid arthritis (RA), an autoimmune disease of complex etiology, is an ailment that inflicts considerable physical, psychological and economic burden on the patients and care-providers. Progress of the disease, coupled with inadequate control through medications, leads to irreversible joint damage. Although NSAIDs, corticosteroids and other DMARDs (disease-modifying antirheumatic drugs) have been used for treating RA, they have their limitations in terms of tolerability, toxicity and disease-modifying effect. In this scenario, plant-based formulations provide a unique modality of treatment of RA as they are safe and have a disease-modifying action. The present study was conducted to evaluate the efficacy of a multi-ingredient formulation "Arthrella" in comparison with diclofenac sodium in reducing the pain and inflammation characteristics of RA. Eighty patients were included in the study. In the Arthrella group, the pain score at rest decreased from a mean of 61.8 at baseline to 40.27 at 8 weeks compared to a decrease from a mean of 61.05 to 35.7 in the diclofenac group. The mean pain index on joint movement declined from 61.38 to 38.88 in the Arthrella group, while it decreased from 59.1 to 31.84 in the diclofenac group. The mean reduction in the WOMAC score was 4.80 for patients in the Arthrella group, while it was 4.65 in patients in the diclofenac group. Both the drugs were well-tolerated. It was concluded that Arthrella showed a comparable efficacy versus diclofenac, a standard, well-used NSAID. If the safety aspect is considered, Arthrella definitely has an edge while having an equivalent efficacy.

Plant-based formulations provide a unique modality of treatment of rheumatoid arthritis as they are safe and have a disease-modifying action. Arthrella tablets can be used for reducing the pain and inflammation of rheumatoid arthritis.

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Introduction

Onset of RA can occur as early as 16 years of age; however, most patients are afflicted in midlife[1-4]. The main consequences that result from the autoimmune process of the disease include synovial inflammation and joint damage in the form of bone and cartilage destruction[3,5]. Failure of medical

treatment to decrease joint deterioration ultimately may lead to expensive procedures such as total joint replacement[1,3].

The present study was conducted to evaluate the efficacy of "Arthrella" in reducing the pain and inflammation characteristics of RA. Arthrella is a multi-ingredient formulation that is useful as a natural DMARD. In this study, the therapeutic benefits and the tolerability of Arthrella tablets have been compared with diclofenac sodium.

Materials and methods

Patients diagnosed with RA having acute pain, swelling and joint inflammation, controlled with synthetic NSAIDs, and who required maintenance treatment to prevent recurrence and to minimize joint stiffness and swelling were included in the study. RA test was performed at baseline for all patients enrolled in the study. However, RA-negative patients with clinical features of RA were also enrolled. Patients with acute flare, overt joint deformity, joint pain following trauma, patients who required surgical intervention and patients with history of gastritis, peptic ulcer and bleeding ulcers were excluded from the study.

Eighty patients diagnosed as suffering from RA who needed drug therapy were enrolled in the study. A written informed consent was obtained from all patients before enrolling them in the study. They were divided into two groups: Group A patients were administered tablet Arthrella in a dose of one tablet twice daily, while Group B patients were administered tablet diclofenac 50 mg twice daily for a minimum period of 12 weeks. Evaluation of patients was performed every 15 days. Patients who were on other medications underwent a washout period of 15 days, following which they were started on one of the two drugs. The two preparations were made to appear identical and were blinded.

Evaluation parameters

Following are the parameters on which the efficacy of the drugs was evaluated:

Objective parameters: Joint swelling, mobility of the joint and Ritchie's index for joint tenderness. The pain at rest and on joint movement was evaluated on a visual analog scale (VAS). The WOMAC score was also used.

Subjective parameters: These were pain, stiffness and a feeling of well-being. For assessing the tolerability of the medicine, epigastric burning/ pain were recorded. Adverse effects were also recorded and monitored.

Results

A total of 73 patients completed the trial. Table 1 summarizes the baseline characteristics of the patients in the two groups.

Pain at rest

In the Arthrella group, the pain at rest measured on a VAS, decreased from an average of 61.8 at baseline to 40.27 at 8 weeks. In the diclofenac group, the pain index decreased from an average of 61.05 to 35.7. The results in the two groups were comparable (p value not significant) (Fig. 1).

Pain on joint movement

The baseline average pain index on VAS declined from 59.1 to 31.84 in the diclofenac group,

Table 1
Age/sex and clinical parameters in two groups

	Arthrella = 36	Diclofenac = 38	p value
Male	17	18	—
Female	19	20	—
Age (yrs)	53.05	49.17	>0.05
Weight (kg)	64.05	63.97	>0.05
Height (cm)	157.08	154.02	>0.05
Pulse rate (per minute)	81.97	78.97	>0.05
Systolic blood pressure (mmHg)	125.88	124.89	>0.05
Diastolic blood pressure (mmHg)	82.11	80.31	>0.05

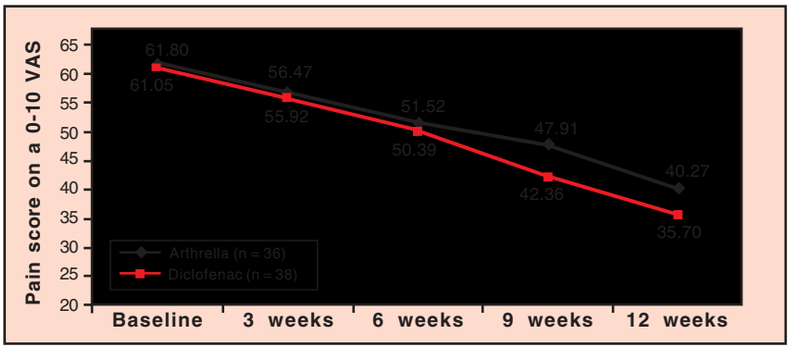

Figure 1. Pain on a 0-10 VAS at rest in two treatment groups at baseline and after 3, 6, 9 and 12 weeks of therapy.

while it decreased from 61.38 to 38.88 in the Arthrella group. In this parameter also, the results between the two groups were comparable (p value not significant) (Fig. 2).

Fall in pain score

As is evident in Figure 3, the fall in pain score at rest and on joint movement was initially equivalent in the two groups. However, at the end of the study, the patients in the diclofenac group had a marginally higher fall in pain score.

Reduction in WOMAC score:

The mean reduction in the WOMAC score was 4.80 for patients in the Arthrella group, while it was 4.65 in patients in the diclofenac group. Thus, there was no statistically significant difference between the two study medicines in reducing the WOMAC score (p value not significant (Fig. 4).

Global efficacy by physicians

At the end of the study, four patients in the Arthrella group were rated as showing very good response, 31 patients were rated as good and one patient as fair. For the diclofenac group, three patients were rated to show a very good response, while 35 patients had good response.

Tolerability assessment by physicians

Three patients in the Arthrella group were assessed to have very good tolerability to the study drug, while 30 patients showed good tolerability and three patients showed fair tolerability. In the diclofenac group, two patients showed very good tolerability, 31 good tolerability and five fair tolerability.

Discussion

RA is a chronic, systemic, inflammatory disease that chiefly affects the synovial membranes of multiple joints in the body. Because the disease is systemic, there are many extra-articular features of the disease as well. In most cases of RA, the patient has remissions and exacerbations of the symptoms. It is important to realize that there are very few patients that have complete remission of the disease.

RA is an autoimmune disease that is acquired and in which genetic factors appear to play an important role. The presence of HLA-DR4 antibody in 70% of patients with RA lends support to the genetic predisposition to the disease. Rheumatoid factor(s) are antibodies to IgG, and are present in 60-80% of adults with the disease.

The prevalence of the disease is 1-2% of the general population and is observed worldwide. Females with RA outnumber males by a ratio of 3:1. Onset of the disease in adults is usually between the ages of 40-60 years, although it can occur at any age.

There are several different classes of drugs utilized to treat patients with the various types of

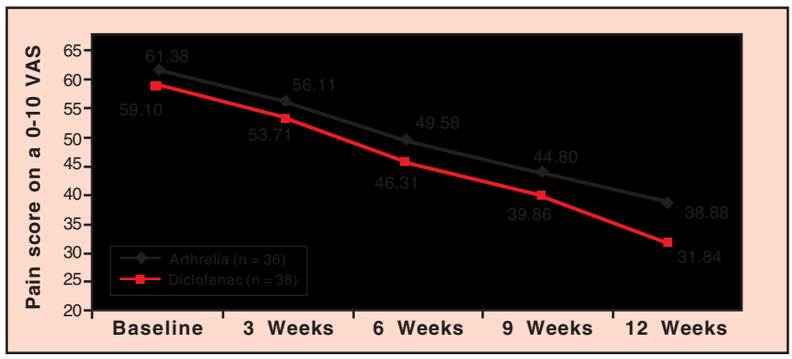

Figure 2. Pain on a 0-10 VAS during joint use/mobility in two treatment groups at baseline and after 3, 6, 9 and 12 weeks of therapy.

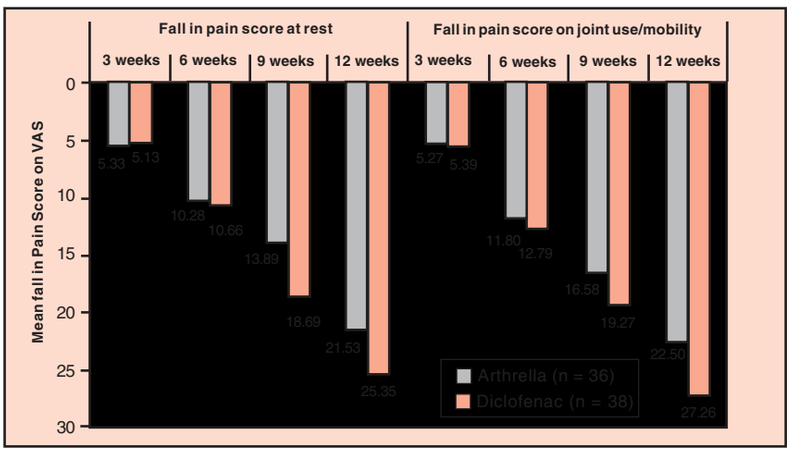

Figure 3. Fall in pain score on 0-10 VAS in the two treatment groups at 3, 6, 9 and 12 weeks of study period.

rheumatic disease. These classes include analgesics to control pain, corticosteroids, uric acid-lowering drugs, immunosuppressive drugs, NSAIDs and DMARDs. NSAIDs are usually the first class of drugs prescribed and the most commonly used.

Against this background, it is significant that the limitations of NSAID treatment are considered very carefully before instituting therapy. Many times, patients develop adverse effects to NSAIDs, given the necessity for prolonged treatment. The availability of a natural, well tolerated and clinically effective medicine will be of immense benefit to mitigate the pain, joint stiffness and inflammation in patients with longstanding RA.

One such product is Arthrella - a herbomineral formulation, which contains Shallaki guggul (*Boswellia serrata*), Gold, Nirgundi (*Vitex negundo*) and Ernad (*Ricinus communis*). In this randomized, comparative trial, it is noteworthy that Arthrella has shown a comparable efficacy vis-a-vis diclofenac - a standard, well-used NSAID. On all evaluation parameters, it was observed that Arthrella and diclofenac showed similar results. In the reduction in pain score, patients on diclofenac showed a greater benefit. However, if the safety aspect is considered, the risk benefit ratio of both the study medicines will be equivalent, with Arthrella having a definite edge on the safety parameter.

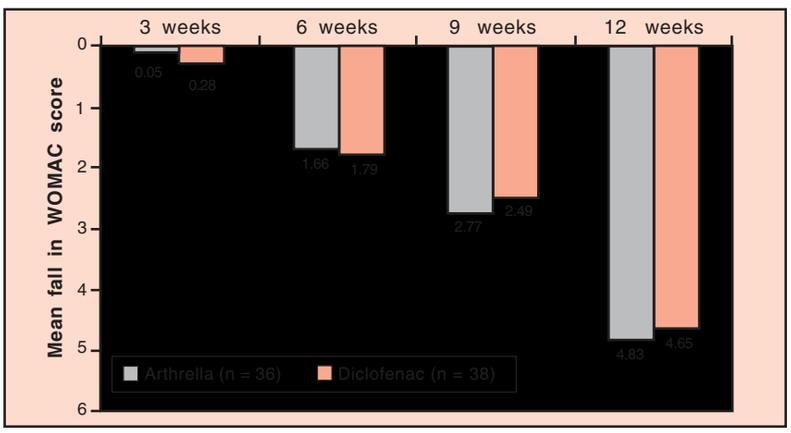

Figure 4. Reduction in mean WOMAC score in the two treatment groups at 3, 6, 9 and 12 weeks of study period.

B. serrata, a major ingredient of Arthrella, is a moderate to large branching tree found in India, Northern Africa and the Middle East. It yields a gummy oleo-resin which contains oils, terpenoids and gum. Upto 16% of the resin is essential oil, the majority being alfa thujene and p-cymene. Studies on experimental models in India have shown that ingestion of a defatted alcoholic extract of *Boswellia* acts as a DMARD through a decrease in polymorphonuclear leukocyte infiltration and migration, decrease in primary antibody synthesis[6-8], and an almost total inhibition of the classical complement pathway.

In vitro testing has revealed that *Boswellia* specifically, and in a dose-dependent manner, blocks the synthesis of pro-inflammatory 5-lipoxygenase products, including 5-hydroxyeicosatetraenoic acid and leukotriene B4.

The other ingredients of Arthrella are Nirgundi (*V. negundo*) and Erand (*R. communis*), which have well known anti-inflammatory action. Fresh leaves of *V. negundo* exert anti-inflammatory and pain-suppressing activities possibly mediated via

Conclusion

From this trial, it can be concluded that the clinical efficacy of Arthrella tablets is comparable to that of diclofenac sodium. Arthrella tablets can be used for reducing the pain and inflammation of RA. The efficacy of the drug in the management of RA can be attributed in part to its anti-inflammatory action as also to its disease-modifying activity. No side-effects of Arthrella were reported by the patients in this trial.

prostaglandin synthesis inhibition, antihistaminic activity, membrane stabilizing and antioxidant activities[9].

Arthrella also contains gold, which also acts as a DMARD. Gold salts have been used since a long time in the treatment of inflammatory arthritis. Although the exact mechanism of action of gold is not well understood, in patients with inflammatory arthritis, such as adult and juvenile RA, gold salts have been shown to decrease the inflammation of the joint lining. This effect can prevent destruction of bone and cartilage. Gold salts are often used as second-line drugs when the arthritis progresses in spite of the use of anti-inflammatory drugs (NSAIDs and corticosteroids).

In a 5-year prospective controlled trial conducted on 137 patients with early RA (<2 years' duration) to test the benefit of early therapy with a gold salt (auranofin)[10], it was found that at 2 years, early gold therapy resulted in significant benefits with respect to clinical and radiological endpoints. A sample of 75 of these patients were followed-up for 5 years and these benefits of early gold therapy were maintained[11].

However, treatment with auranofin can result in side effects at any time during treatment or months after treatment has been discontinued. The most common adverse reactions to auranofin are diarrhea, skin rashes and itching. Auranofin can also cause metallic taste and mouth sores. Since gold salts can cause serious kidney and bone marrow damage, all patients require regular blood and urine test monitoring. Rarely, patients can have severe allergic reactions to auranofin resulting in shock. In addition, detrimental effects of auranofin on the levels of antioxidant enzymes such as glutathione peroxidase have also been reported[12].

Ayurvedic gold preparations, in comparison, have been used extensively for the treatment of RA without such serious side effects. Recently, various studies have been conducted to provide insights about the disease-modifying activity of Ayurvedic gold formulations in RA. In one such study, the effects of an Ayurvedic gold preparation were evaluated on non-specific immunity in mice. Auranofin was studied for comparison. Male mice were administered with incremental doses of these drugs orally for 10 days. Parameters of study included body weight, organ weight, peritoneal exudate cell (PEC) counts and phagocytic activity of PEC. The results indicated that the Ayurvedic gold preparation significantly improved immune function as compared to auranofin. This is an interesting observation and gives a rational basis to the claims of efficacy and safety of gold preparations[13]. In addition, experimental models chronically treated with gold preparations have shown significantly increased superoxide dismutase and catalase activity, two enzymes that reduce free radical concentrations in the body[14].

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