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Indian Journal of
CLINICAL
PRACTICE

IJCP

Special Reprint 2013

A Phase-II Clinical Trial of Antarth Plus, a Phytomedicine to Assess its Efficacy and Safety in Osteoarthritis

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ABSTRACT

Antarth Plus, a polyherbal phytomedicine of M/S Millennium Herbal Care Limited, was studied for its efficacy and safety in patients with osteoarthritis (OA). A total of 30 patients of either sex and above the age of 18 years who were diagnosed clinically and radiologically as OA for not >2 years and who were not responding to any other treatment, who have taken cartilage protective medication for <2 months or have completed 2-month course >6 months back but did not respond were included in the study. Patients suering from other types of arthritis or other conditions like hyperacidity, peptic ulcers, gastritis, renal failure, liver disorders, etc. and those on oral or injectible steroids, oral contraceptives and pregnant and lactating women were excluded from the study. Antarth Plus was given as two tablets twice-daily each time for six months and patients were evaluated every month. VAS was used to assess pain; pain during functional disability was assessed every month. The severity of pain was reduced by 65.35%, which was highly significant. Out of the four parameters of functional disability of joint score, pain during walking distance was reduced by 71.10%; during squatting was reduced by 63.29%; during sitting crosslegged by 66.15% and during climbing stairs by 42.17%. All these differences were highly significant. In global assessment, both patients and physician were highly satisfied with this treatment. Antarth Plus is very effective in controlling OA pain. It did not produce any adverse events and hence is very safe.

Key words: Osteoarthritis, pain, visual analogue scale, functional disability

Due to changed lifestyle such as lack of exercise and changed food habits, lifestyle disorders such as arthritis, asthma, hypertension and diabetes are very common particularly amongst urban population. Arthritis affects people of all ages, but is more common in older people. The condition can significantly impair a person's ability to do everyday activities. Arthritis is not a single disease, but a group of over 100 conditions that cause pain, stiffness and/or swelling of the joints. Pain, stiffness and loss of mobility are indications of joint disorders. This may be due to a wide variety of disorders such as osteoarthritis, (OA), rheumatoid arthritis, cervical and lumbar spondylitis, etc. Medical management of these conditions is predominantly with the use of nonsteroidal

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anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and many more. However, till date there is no complete remedy for the cure of this disease. Alternative systems of medicine such as Ayurveda claim to have remedies for such chronic conditions but without sufficient documentary evidence. The present study is an attempt to validate these claims.

Material and Methods

The study was initiated after obtaining the approval of the protocol by the Institutional Ethics Committee (IEC). Patients' written informed consent was obtained before enrolling in the study.

Patients

After recording demographic data such as age, sex, etc, history, signs and symptoms and clinical examination, patients were selected on the basis of following criteria.

Male or female adult patients who were above 18 years of age, clinically and radiologically diagnosed as OA, suffering from OA for not >2 years, who were only on NSAIDs and not responding to any other treatment, who had taken cartilage protective medication [Glucosamine ± Chondroitin preparations or methylsulfonylmethane (MSM) preparations] for <2 months or had completed two-months course >6 months back but did not respond were included in the study. Patients with following disorders were excluded: Hyperacidity, peptic ulcers, gastric ulcers, gastritis, renal failure, liver disorders, other types of arthritis such as rheumatoid arthritis, gout, pseudogout, psoriatic arthritis and Reiter's syndrome. Patients on long-term steroid treatment or surgical interventions, on oral contraceptives, pregnant and lactating women were also excluded from the study.

Method

The patients were given 60 capsules at each visit and were asked to take two capsules in the morning after breakfast and two in the evening after dinner for a period of six months. Patients were asked to visit the centre every month for follow up. Compliance was tested by counting the number of capsules remaining at the end of each month. Laboratory investigations (CBC, LFT, RFT) were carried out before and after the treatment to assess the safety of medication. Patients were also given diclofenac sodium 50 mg tablets and were asked to take one tablet in the morning and one tablet in the evening as a rescue medication, if required and keep a record of the tablets taken. Similarly, ranitidine was also given as rescue medication. Patients were assessed for pain in general using Visual Analogue Scale (VAS) and during functional disability were assessed as 0-mild, 1-moderate, 3-severe and 4-acute unbearable pain. Patients' and Physician's Global assessment was scored as 1-Poor, 2-Good and 3-Excellent.

Results

All the 30 patients who were enrolled for the study completed the six-month treatment without a break and hence their data was taken for analysis. There were 9 male and 21 female patients and their mean age was 56.83 ± 7.78 and the range was 42-74 years. Their vitals were normal before treatment. After six months treatment there was a slight decrease in respiratory rate which was not significant. From a basal value of 20.30 ± 1.02 per minute, it reduced to 19.67 ± 1.32 per minute. There were no changes in other vital parameters. As regards efficacy of Antarth Plus in primary efficacy variables, the severity of pain in general measured on VAS, the initial score was 5.57 ± 1.33 (Mean ± SD) before treatment which reduced to 1.93 ± 0.83 after six months, which is a total reduction of 65.35% (Tables 1 and 2). This was statistically highly significant ($p < 0.001$). The reduction started from the first month itself and gradually reduced by about 65% by the end of treatment at six months.

Functional disability of the joint was assessed by measuring pain during different functions viz. Walking distance, while squatting, while sitting crosslegged and while climbing steps. The results are shown in Tables 1 and 2 including Fig. 1.There was a significant reduction in pain, after treatment, while performing these activities. Pain while walking was reduced by 71.1%, while on squatting, it reduced by 63.29%. Pain while sitting crosslegged reduced by 66.15% and during climbing steps by 42.17%. All these reductions were highly significant ($p < 0.001$).

In secondary efficacy parameter, consumption of rescue medication, diclofenac, was also significantly reduced after six months treatment. From an initial mean value of 7.52 tablets/month, it reduced to 3.23 tablets/month, a reduction of 57.05%. None of the patients required ranitidine during the course of the study.

In global assessment, both the patients and physician had almost similar opinion about the efficacy and safety of Antarth Plus (Fig. 2). About 23% of patients said the treatment was excellent; about 50% said it was good;

Table 1. Effect of Antarth Plus on Efficacy Parameters (Before and After Treatment)

Efficacy variable	Day 0 Mean ± SD	Day 180 Mean ± SD	Reduction	Percentage reduction (%) to basal
Severity of pain VAS (0 - 10)	5.57 ± 1.33	1.93 ± 0.83	3.64	65.35*
Pain while walking (0-4)	1.70 ± 1.18	0.50 ± 0.63	1.23	71.10*
Pain during squatting (0-4)	2.27 ± 0.87	0.87 ± 0.57	1.50	63.29*
Pain while sitting crosslegged (0-4)	2.47 ± 0.99	0.87 ± 0.63	1.70	66.15*
Pain while climbing stairs (0-4)	2.27 ± 0.74	1.33 ± 0.71	0.97	42.17*
No. of diclofenac tablets taken	7.52 ± 3.51	3.23 ± 1.85	4.29	57.05*

*p < 0.001

Table 2. Month-wise Effect on Efficacy Variables (Mean ± SD)

Parameter	Day 0	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months
Severity of pain, general VAS (0-10)	5.57 ± 1.33	4.67 ± 1.27	4.17 ± 1.34	3.50 ± 1.20	2.93 ± 1.08	2.33 ± 0.88	1.93 ± 0.83
Pain while walking	1.70 ± 1.18	1.60 ± 1.16	1.30 ± 1.12	1.10 ± 1.09	0.80 ± 0.89	0.50 ± 0.73	0.50 ± 0.63
Pain during squatting	2.27 ± 0.87	1.90 ± 1.03	1.77 ± 0.90	1.43 ± 0.63	1.23 ± 0.63	1.00 ± 0.63	0.87 ± 0.57
Pain while sitting crosslegged	2.47 ± 0.90	2.27 ± 0.87	2.03 ± 0.93	1.77 ± 0.77	1.33 ± 0.80	1.03 ± 0.85	0.87 ± 0.63
Pain while climbing	2.27 ± 0.74	2.13 ± 0.90	2.13 ± 0.90	1.93 ± 0.74	1.73 ± 0.74	1.57 ± 0.86	1.33 ± 0.71

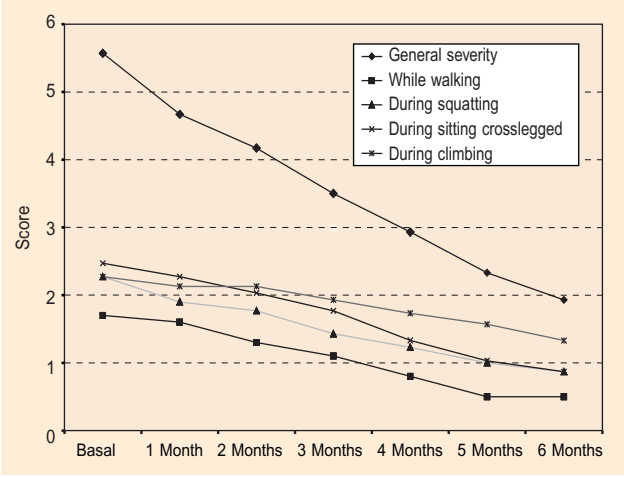

Figure 1. Effect of Antarth Plus on pain during activities.

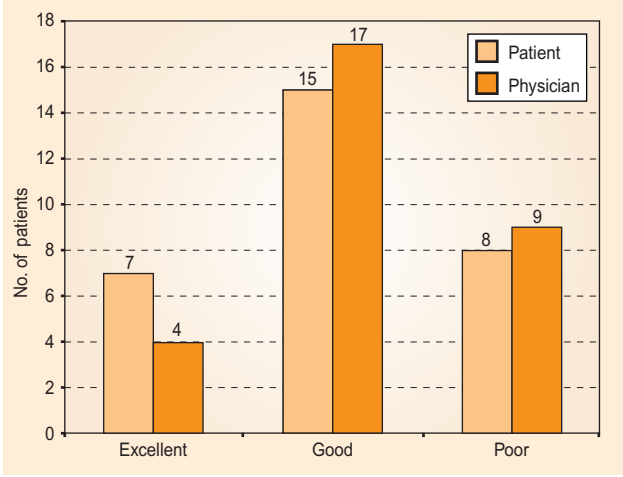

Figure 2. Global assessment.

only about 27% described it is poor. According to the physicians, about 13% of patients had excellent results, about 57% had good and about 30% had poor response. Overall, the patients and the physicians appeared to be in agreement with the results.

Discussion

Osteoarthritis (OA) is the most common form of arthritis in the United States and in India.[1] Patients with OA have pain that typically worsens with weight-bearing activity and improves with rest. The morning stiffness and swelling of the involved joint after periods of inactivity are also very common. On physical examination, they often have tenderness on palpation, bony enlargement, crepitus on motion, and/or limitation of joint motion. Unlike rheumatoid arthritis and other inflammatory arthritis, inflammation, if present, is usually mild and localized to the affected joint. Although the causes of OA are not completely understood, biomechanical stresses affecting the articular cartilage and subchondral bone, biochemical changes in the articular cartilage and synovial membrane and genetic factors are all important in its pathogenesis.[2-4]

Although there is no known cure for OA, treatment designed for the individual patient can reduce pain, maintain and/or improve joint mobility and limit functional impairment. In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee.[5,6] Those guidelines outlined the use of nonpharmacologic modalities, including patient education and physical and occupational therapy, the foundation of treatment of individuals with OA, as well as the use of pharmacologic agents.

The goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality-of-life, with avoidance, if possible, of toxic effects of therapy. Individuals with OA of the lower extremity may have limitations that impair their ability to perform activities of daily living (ADLs), such as walking, bathing, dressing, use of the toilet and performing household chores. While physical therapy and occupational therapy play central roles in the management of patients with functional limitations, use of pharmacotherapy is essential to reduce pain during these activities. The most commonly used drug for this is acetaminophen. But the drug is known to produce hepatotoxicity at higher doses and hence cannot be used for a longer time and in patients with impaired liver function and chronic alcoholics.[7-9] Alternatively, NSAIDs are the drugs of choice in the treatment of OA and have been shown to be more effective than acetaminophen in several clinical trials. However, these drugs also have serious adverse effects on gastrointestinal systems which are very common. They produce severe acidity leading to ulceration and bleeding. Data from epidemiologic studies show that among persons aged 65 years, 20-30% of all hospitalizations and deaths due to peptic ulcer disease were attributable to therapy with NSAIDs.[10-12] More recently, cyclooxygenase-2 COX-2 inhibitors celecoxib, rofecoxib have been shown to be more effective; they also have fewer GI side effects[13,14] than NSAIDs. However, COX-2-specific inhibitors can cause renal toxicity. Caution must be exercised, therefore, if they are used in patients with hypertension, congestive heart failure or mild-to-moderate renal insufficiency; they should not be used in patients with severe renal insufficiency. In addition, the use of celecoxib is contraindicated in patients with a history of an allergic reaction to a sulfonamide. Some recent placebo-controlled trials show an increased risk of serious thrombotic cardiovascular events, which can be fatal with COX-2 selective NSAIDs, particularly when used at higher doses. Because of the increased risk of these cardiovascular events, one COX-2 inhibitor, rofecoxib, was voluntarily removed from the market by the manufacturer in September 2004. Other COX-2 selective NSAIDs are under evaluation by the USFDA.

Arthritis is a chronic disease which has no cure. Only symptomatic relief can be obtained by use of medications. But drugs available are not safe for long-term use. Hence, there is a need for an effective and safe remedy. The alternative systems of medicine claim to have such remedies. Antarth Plus is one such product developed by M/S Millennium Herbal Care Limited based on the principles of Ayurveda for the treatment of arthritis.

In the present study, Antarth Plus has shown a very good effect in relieving pain in general and during performing some functions, in patients with OA. The constant pain makes the patients miserable. It is compounded with more severity of pain while performing some activities like walking, squatting, sitting crosslegged and even while climbing steps. Thus, their quality-of-life is adversely affected.

A 65% reduction of pain in general after six months treatment with Antarth Plus is a great relief to the patients. The treatment has also indicated a significant reduction in pain during daily routine activities like walking, sitting, climbing, squatting, etc. A 71% reduction in pain while walking, 63% while squatting, 66% while sitting crosslegged and 42% while climbing steps indicates that the drug is very effective in controlling pain This reduction in pain vastly improves the quality-of-life in patients.

There was a significant reduction in consumption of the rescue medication, diclofenac. Diclofenac, a COX-2 inhibitor, offers immediate relief from pain to the patients, but the effect is not long-lasting. The patient may have to keep taking it to keep the pain under control. This will definitely have some adverse event in the long run. It is claimed that herbal drugs do not produce instant relief unlike allopathic drugs, but produce a slow and sustained relief. So, in the initial stages patients were allowed to take diclofenac as a rescue medication to get instant relief, if the pain was unbearable. There was a significant reduction (57%) in consumption of this rescue medication after treatment with Antarth Plus. Since 27% of patients were not satisfied with the treatment, they may be the ones who

continued to take diclofenac. None of the patients who were taking Antarth Plus for six months needed to take ranitidine as they did not experience any GI disturbance during or after treatment. This indicates that the drug is very safe.This is further supported by the fact that no patient reported any adverse events during treatment.

In global assessment, majority of the patients were satisfied with the treatment. While 23% said it is excellent and 50% said it is good, only 27% were not satisfied. Physicians' opinions were almost same as those of patients.

Conclusion

The present study indicates that Antarth Plus is very effective in the treatment of patients with OA. It effectively reduces pain in general and during normal daily activities thus improving the quality-of-life in patients. The drug is very safe and does not produce any adverse events on long-term treatment.

Acknowledgements

The authors thank M/S Millennium Herbal Care Limited for supply of study medication.

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