Original Article

Efficacy and Tolerability of Oral Enzyme Therapy as Compared to Diclofenac in Active Osteoarthrosis of Knee Joint : An Open Randomized Controlled Clinical Trial

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Abstract

- **Objective : To compare the efficacy and tolerability of an oral enzyme preparation (Phlogenzym) with that of an NSAID (diclofenac) in the treatment of active osteoarthrosis.**
- **Methods : Prospective, randomized, controlled, single-blind study of seven weeks duration at a tertiary care centre wherein 50 patients aged 40-75 years, with activated osteoarthrosis of knee joint were randomized to receive phlogenzym tablets (2-3 tablets, bid) or diclofenac sodium 50 mg bid for three weeks.**
- **Results : At the end of therapy (three weeks) and at follow-up visit at seven weeks there was reduction in pain and joint tenderness and swelling in both groups, and slight improvement in the range of movement in the study group. The reduction in joint tenderness was greater ($p < 0.05$) in the study group receiving phlogenzym.**
- **Conclusion : Phlogenzym is as efficacious and well tolerated as diclofenac sodium in the management of active osteoarthrosis over three weeks of treatment. (JAPI 2001; 49 : 617-621)**

Introduction

Osteoarthrosis (OA) of the knee joint is the most prevalent cause of disability, especially in older patients.[1] It is a degenerative process that results from metabolic, mechanical, genetic and other influences.[2] There is increasing evidence that immune, system dysfunction contributes to the pathophysiology of OA.[3-6]

OA is characterized by progressive loss of articular cartilage and bony overgrowth. Because cartilage is not innervated, the pain of OA rises from secondary effects, such as synovial inflammation, joint capsule distention, and stretching of the periosteal nerve endings.

The most commonly used drugs for the palliative treatment of OA are the non-steroidal anti-inflammatory drugs (NSAIDs).[7] Diclofenac sodium is one of the widely used among these. It provides relief from pain and inflammation and restores mobility of the affected joints but is associated with severe side-effects (dyspepsia, upper abdominal pain, gastrointestinal bleeding) following medium-to long-term use.[8-10]

In a randomized, double-blind study, Singer[11] compared the efficacy of an oral enzyme preparation (Wobenzym; Mucos Pharma GmbH, Geretsried, Germany; each enteric-coated tablet contained pancreatin 100 mg, trypsin 24 mg, chymotrypsin 1 mg, bromelain 45 mg, papain 60 mg and rutin 50 mg) in activated OA of the knee joint with that of diclofenac. Five week's treatment with either Wobenzym (seven tables qid) or diclofenac (50 mg twice daily) resulted in equivalent improvement in range of movement of the joint and early morning stiffness, pain at rest, pain following exercise, nocturnal pain and joint tenderness.[11]

Material and Methods

The study protocol was approved by the institution's ethics committee. Informed written consent was obtained from all patients.

Patient eligibility : Fifty adult patients with active arthrosis of the knee joint and X-ray verified reduction in interarticular space, were evaluated for inclusion in this open study. Complete clinical evaluation plus hemogram, liver and renal biochemistry were done in all cases. Exclusion criteria included current or recent (less than two weeks) antirheumatic therapy, arthroses secondary to systemic disease, suspected bacterial infection of the joint, existing pregnancy and lactation, known hypersensitivity to

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active principles or auxillary substances of test preparates. Patients with hemorrhagic disorders and who had undergone corticosteroid or anticoagulant therapy in the last two months were also excluded.

Drug intervention : Patients were randomized into two groups. The study group received phlogenzym, three tablets twice daily for the first week while in the next two weeks the dose was reduced to two tablets, twice daily. Patients in the control arm received 50 mg diclofenac sodium, (Voveran; Novartis, India.) one tablet twice daily for three weeks.

Evaluation : Patients were evaluated at baseline, at three weeks of therapy and again at four weeks after cessation of therapy by the investigators who were different from the one dispensing the medications. Pain at rest and pain on movement were assessed subjectively as none, mild, moderate and severe. Improvement in pain is defined as any change from baseline to 1st follow - up and thence to 2nd follow up from severe to moderate, moderate to mild and mild to no pain. Joint tenderness was assessed as none, slight (patient reports pain on applying finger pressure), moderate (patient winces), severe (patient winces and withdraws) and very severe (patient would not allow examination for tenderness). Improvement in tenderness is defined in the same manner as assessed for pain. Joint swelling was measured with a tape to the nearest cm at the level of the upper patellar margin at full extension of the knee. Improvement in swelling is reduction in cms over previous reading. Range of movement was measured at the knee joint using a goniometer. The range was defined as the difference between full unassisted extension and full unassisted flexion. The patients were also categorized as ARA class I, II or III at each evaluation. Subjective global assessment was done independently by the physician and patient and graded as poor, good or very good.

Safety evaluation : Safety of drugs was evaluated at baseline and at follow-up visits in the two groups. Haemogram, blood urea, creatinine, total bilirubin, SGOT, SGPT, alkaline phosphatase and urinalysis for albumin and glucose were tested at each visit.

Statistical methods : Statistical analysis was done using the chi-square test. The primary efficacy variables were defined as number of patients who showed improvement following therapy.

Results

Presenting features : Of 50 patients enrolled in the study, 25 (eight men; mean age 56 years) were in the study group and 25 (11 men; mean age 58.7 years) in the control group. Patients were comparable with respect to their presenting features. In the study group, 15 patients had their left knee affected and 10 patients had their right knee affected; corresponding figures in the control group were eight patients and 17 patients. All patients showed narrowing of joint space on X-ray. Osteophytes were present in 19 patients in the study group and 15 patients in the control group.

Efficacy evaluation : Post-treatment data were available for all patients. Improvement in pain at rest, pain on movement and joint tenderness was seen in both groups at the end of treatment and at the follow-up visit (Table 1).

Eighteen patients in the study group had reduction in joint tenderness at the end of therapy as compared to 10 in the control group ($p < 0.05$). At follow-up four weeks after, 19 patients in the study group showed reduction in joint ten-

Table 1 : Comparison of mean score of pain (pain at rest, pain on movement, and joint tenderness between enzyme and diclofenac)

Parameters	Baseline		End of therapy		Follow up period	
	Study	Control	Study	Control	Study	Control
Pain at rest						
Mean	1.12	1.24	0.64	0.92	0.56	0.84
SD	0.73	0.78	0.70	0.76	0.77	0.71
% of change from baseline	-	-	42.9	25.8	50.0	32.2
Pain on movement						
Mean	1.92	2.04	1.16	1.32	1.20	1.20
SD	0.70	0.67	0.62	0.75	0.65	0.76
% of change from baseline	-	-	39.6	36.3	37.5	41.2
Joint tenderness						
Mean	1.64	1.44	0.80	1.16	0.80	1.04
SD	0.81	0.65	0.58	0.62	0.64	0.64
% of change from baseline	-	-	*51.2	19.5	*51.2	27.8
Joint swelling						
Mean	41.9	40.84	40.0	40.0	39.95	40.55
SD	8.67	12.55	6.45	11.92	6.95	12.51
% of change from baseline	-	-	4.5	2.1	4.6	1.0

* $P < 0.05$ significant

By Mann Whitney U Test at 5% level of significance; joint swelling compared by student t test.

Table 2 : Global evaluation of efficacy and tolerability by physicians and patient in patients who received phlogenzym (S) and those who received diclofenac (C) for activated osteoarthrosis

	Global evaluation by physicians					
	Postreatment			Follow-upperiod		
	Poor	Good	V. Good	Poor	Good	V. Good
Study	02 (08)	18 (72)	05 (20)	05 (20)	17 (68)	03 (12)
Control	04 (16)	02 (08)	19 (76)	03 (12)	15 (60)	07 (28)
	Global evaluation by patients					
	Postreatment			Follow-upperiod		
	Poor	Good	V. Good	Poor	Good	V. Good
Study	0	20 (80)	05 (20)	05 (20)	15 (60)	05 (20)
Control	04 (16)	17 (68)	04 (16)	01 (04)	18 (72)	06 (24)

derness, while only 11 in the control group showed similar improvement ($p < 0.05$). (Table 1). Reduction in joint swelling at the end of therapy was similar in both groups. (Table 1)

Number of patients showing improvement in pain at rest and pain on movement was 12 and 17 in the study group and nine and 15 in the control group. Four weeks later, 15 patients in the study group and 10 in the control group showed improvement in pain at rest. The improvement in pain on movement was similar in the two groups. (Table 1).

There was no change in the range of movement (flexion and extension) in either group.

The number of patients in ARA class I (n=6), II (n=14) and III (n=5) showed a trend towards improvement in the study group (7, 17, 1 respectively after treatment and at follow-up) but this was not statistically significant. Corresponding figures in the control group were 5, 17, 3 before treatment and 5, 16, 4 after treatment and at follow-up.

Subjective evaluation of efficacy and safety by doctors and patients at the end of treatment showed improvement of 10 and 12 patients in the study group compared to nine and eight in the control group. Four weeks later, the global evaluation by doctors and patients showed improvement of 12 and 13 patients in the study group compared to eight and eight in the control group (Table 2).

There was no alteration in the laboratory parameters in the two groups at any visit.

Discussion

Osteoarthrosis (OA) is characterized by progressive loss of articular cartilage and bony overgrowth and is seen mostly in elderly individuals. The initially bland progression of OA may become clinically relevant as an inflammation brought about by the increasing deposition of ground-down cartilaginous debris.[12] For the patient, the most important aspect of the condition is pain and the associated impairment of movement.[13] Because cartilage is not innervated, the pain rises from secondary effects, such as synovial inflammation and fluid accumulation leading to joint capsule distention and stretching of the periosteal nerve endings.

Diclofenac sodium is one of the most widely used NSAIDs for the treatment of OA. Although the drug provides relief from pain and inflammation and restores mobility of the affected joints, it is associated with severe side-effects. Jones reported a post marketing surveillance study of a sustained release form of diclofenac on 7438 osteoarthritic patients; adverse effects led to withdrawal from the drug therapy in 18% of the patients.[10] In another study involving 336 patients with osteoarthritis over six months, Hosie *et al* reported that 31 patients withdrew from the study due to adverse effects following diclofenac therapy.[8]

Phlogenzym is a biological response modifier. Following absorption, it increases the plasma proteolytic activity that accelerates inflammatory reaction, promoting early resolution of edema and early healing. Phlogenzym contains bromelain, trypsin and rutin. Bromelain, a plant protease, breaks down plasma proteins that have exuded into the interstitium, thus exerting an anti-edema action. Trypsin, an animal protease, exerts a fibrinolytic action, thereby improving blood rheology and local blood flow.[14] Rutin stabilizes vascular endothelium and reduces extravasation of fluid from the intravascular space.[15,16] Together the three components of phlogenzym reduce edema and hence the pain induced by the pressure of exudate on nerve endings.[17]

Immune system dysfunction is now being implicated in the pathogenesis of OA. The integrity of articular cartilage is maintained by the balance between cytokine-driven anabolic and catabolic processes. Unregulated or excess influences of these molecules are thought to play a part in the pathophysiology of OA. Two cytokines, IL-1 and TNF alpha, appear to be major culprits in the pathogenesis of synovitis and in cartilage damage in OA.[3] IL-6 seems to be involved in protective mechanisms.[4] Diclofenac

has been shown to aggravate the already imbalanced immune system in patients with OA.[4] Martel-Pelletier *et al* found that there is a two-fold increase in the number of IL-1 receptors in cartilage cells of patients with OA, resulting in their higher sensitivity to stimulation by IL-1. Pelletier *et al* reported that IL-1 stimulates synthesis of metalloproteases (collagenase and stromelysin) leading to a further worsening of the cartilage damage.[5] Pelletier *et al* suggested that in osteoarthrosis chondrocytes are stimulated by IL-1, which may induce expression of NO synthase, leading to NO production. This elevation of NO may contribute to the pathophysiology of OA since it has been shown to reduce the synthesis of IL-1 receptor antagonist (IL-1ra) and thus result in an enhancement of cartilage matrix degradation.[6] Tanaka *et al* reported that they found expressed on the surface of osteoblasts from patients with OA adhesion molecules ICAM-a, VCAM-1, and LFA-3. This is an important observation because these adhesion molecules also function by transducing activation signals that facilitate the production of bone-resorbing cytokines.[18]

Phlogenzym, besides being an anti-edematous anti-inflammatory agent,[17] is also an immunomodulatory agent that down-regulates overexpressed adhesion molecules and cytokines and restores immunohomeostasis. Trypsin and bromelain act on the CH2 domain of ICAM-a, VCAM-1, and LFA-3 and inactivate them; they also break down excess cytokines in the vicinity of the inflammatory site, thereby reducing the intensity of the inflammation.[14] In a study conducted by Triveni *et al*[9] it was shown that proteolytic enzymes induce a dramatic stimulation of neutrophil apoptosis which may play an important role in the normal resolution of inflammation by limiting the autotoxic potential of the neutrophils.

Our study shows that phlogenzym reduces the symptoms of active osteoarthritis as well as diclofenac sodium does. In fact, more patients who received phlogenzym experienced reduction in joint tenderness than those who received diclofenac. Both drugs were equally well-tolerated. Both patients and doctor found the drugs comparable in efficacy and safety.

Improvement in ARA class was not expected since the follow-up duration was short.

The proteases used in systemic enzyme therapy have been shown to reduce the pain in OA. Furthermore, another compound rutin, has proven free radical scavenging properties which could be useful in controlling the enhanced NO activity seen in OA synovium. As the efficacy of the enzymes in controlling pain and inflammation in OA patients has been found to be equivalent to diclofenac, enzyme therapy could be a useful alternative to diclofenac in the treatment of OA patients.

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References

1. **Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, *et al.*** Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving NSAIDs. *Ann Intern Med* 1995; 123 : 241-9.
2. **Srinivas GR, Chichester CO, Barrach HJ, Matoney AL.** Effects of certain antiarthritic agents on the synthesis of type II collagen and glycosaminoglycans in rat chondrosarcoma cultures. *Agents Actions* 1994; 41 : 193-9.
3. **Ruggeri R, Pulsatelli L, Melchiorri C, Da Re R, Focherini MC, Veronesi M, Facchini A.** Differential expression of IL-1 and TNF receptors in inflammatory arthritis and osteoarthritis. *Boll Soc Ital Biol Sper* 1996; 72 : 15-20.
4. **Westacott CI, Sharif M.** Cytokines in osteoarthritis : mediators or makers of joint destruction? *Semin Arthritis Rheum* 1996; 25 : 254-72.
5. **Martel-Pellertier J, McCollum R, Fujimoto N, Obata K, Cloutier JM, Pelletier JP.** Excess of metalloproteases over tissue inhibitor of metalloproteases may contribute to cartilage degradation in osteoarthritis and rheumatoid arthritis. *Lab Invest* 1994; 70 : 807-15.
6. **Pelletier JP, Mineau F, Raynauld JP, Woessner JF Jr, Gunja-Smith Z, Martel-Pelletier J.** Intraarticular injections with methylprednisolone acetate reduce osteoarthritic lesions in parallel with chondrocyte stromelysin synthesis in experimental osteoarthritis. *Arthritis Rhem* 1994; 37 : 414-23.
7. **Hochberg MC, Roy DA, Kenneth DB, Bruce MC, Paul AD, Marie RG, *et al.*** Guidelines for the medical management of osteoarthritis. *Arthritis and Rheumatism* 1995; 38 : 1541-6.
8. **Hosie J, Distel M, Bluhmki E.** Meloxicam in osteo-arthritis : a six month, double-blind comparison with diclofenac sodium. *Br J Rheumatol* 1996; 35 : 39-43.
9. **Laine L.** Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointest Endosc Clin North Am* 1996; 6 : 489-504.
10. **Jones CW.** A post-marketing surveillance study of voltarol 75 mg SR in the primary care setting. *Br J Clin Pract* 1996; 50 : 390-5.
11. **Singer F.** Aktiverte arthrosen knorpelschonend behndeln. Medizinische enym-forschungsgesellschaft e. V. (ed) : systemishee enzymetherapie. 10th symposium. Frankfurt 1990.
12. **Niethard Fu, Pfeil J.** Orthopadie. Hippocrates verlag. Stuttgart 1989.
13. **Mazieres B.** Gonarthroses. *Rev Prat* 1996; 46 : 2193-200.
14. **Guggenbichler JP.** Einfluß hydrolytischer enzyme auf thrombusbidung and thrombolyse. *Med Welt* 1988; 39 277.
15. **Casley-Smith JR, Casley-Smit JR.** The effects of

O-(beta-hydroxy-ethyl) - rutosides (HR) on acute lymphoedema in rats' thighs, with and without macrophages. *Microcirc Endothelium Lymphatics* 1990; 6 : 457-63.

16. **Blumberg S, Clough G, Michel C.** Effects of hydroxyethyl rutosides upon the permeability of single capillaries in the frog mesentery. *Br J Pharmacol* 1989; 96 : 913-9.
17. **Lindner A, Forster O.** Report on the influence of Wobenzym ® on various rat paw edemas. Report on studies by the institute for general and experimental pathology of the university of Vienna 1976.
18. **Tanaka Y, Fukudome K, Hayashi M, Takagi S, Yoshie O.** Induction of ICAM-1 and LFA-3 by taxi of human T-cell leukemia virus type 1 and mechanism and down-regulation of ICAM-1 or LFA-1 in adult-T-cell-leukemia cell lines. *Int J Cancer* 1995; 60 : 554-61.
19. **Trevani AS, Andonnegui G, Giordano M, Nociari M, Fontan P, Dran G, Geffener Jr.** Neutrophil apoptosis induced by proteolytic enzymes. *Lab Invest* 1996; 74 : 711-21.

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