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RESEARCH ARTICLE

AN OBSERBVATIONAL STUDY COMPARING THE EFFICACY AND TOLERABILITY OF TRYPSIN, BROMELAIN, RUTOSIDE AND ZINC COMBINTION WITH DICLOFENAC SODIUM IN PATIENTS SUFFERING FROM OSTEOARTHRITIS KNEE ATTENDING ORTHOPEDIC OPD, GGH, ANANTAPURAMU

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A B S T R A C T

Aim and Objective: The objective of this study is to compare the effficacy of systemic enzyme therapy -Trypsin, Bromelain, Rutoside and zinc combination with diclofenac alone in the management of pain in osteoarthritis knee.

Materials and Methods: Randomized observational comparative study to compare the efficacy and tolerability of systemic enzyme therapy versus diclofenac in patients attending Orthopedic OPD with episodes of OA knee joint.
A total of 50 patients with osteoarthritis knee were included in the study, who were divided into two groups of 25 each. one group received diclofenac alone and the other group received a combination of of Trypsin, Bromelain and Rutoside with zinc. Both the groups were followed up for 6 weeks. The efficacy was determined by WOMAC scores, collected before and after the study period.

Results: The results of the study are as follows. Within our 6 weeks of observation period, WOMAC scores clearly indicate that the systemic enzyme therapy is equally effective as Diclofenac sodium in alleviating pain and reduction of edema. During the study period, both the drugs were well tolerated by both the study groups.

Conclusion: Osteoarthritis is a common painful joint disease, which is effectively treated with NSAIDs, most commonly Diclofenac; but carries the risk of gastric discomfort, gastric and duodenal ulcer and upper GI bleeding. Systemic enzyme therapy is superior in this aspect as they are free from these adverse effects.

INTRODUCTION

Systemic enzyme therapy combinations are widely used as an alternative or a supplementary treatment for painful joint disorders. The medical treatment with proteolytic enzymes is often described as Systemic Enzyme Therapy or SET[1]. SET has many important indications in traumatologic, thrombotic, infectious, inflammatory, immunopathologic and even tumorous processes. Rheumatoid arthritis, activated arthrosis and extraarticular rheumatism represent important and sensitive targets of SET[2]. Systemic enzyme therapy is particularly employed due to its thrombolytic, fibrinolytic and antioedema effects[3].

Trypsin, Bromelain and rutoside

These form an integral part of the systemic enzyme therapy. The Hydrolase trypsin is extracted from porcine pancreas, the endopeptidase bromelain is extracted from the juice of the trunk of the ripe pineapple and the flavonoid rutoside trihydrate is extracted from the seed of Japanese pagoda tree and also from buckwheat seeds. Studies indicate that Trypsin – Bromelain Rutoside combination can be considered as an effective and safe alternative to NSAIDs[4]. Zinc (Zn) is an essential nutrient required for cell growth, differentiation, and survival, and its deficiency causes growth retardation, immunodeficiency, and other health problems. Zinc is required for over 300 different cellular processes and therefore zinc homeostasis must be tightly controlled in individual cells.[5,6]

In addition, the antioxidant properties of zinc in biochemical systems have been clearly demonstrated and appear to be independent of zinc metalloenzyme activity.[7] Zinc has also been shown to play a significant part in the wound healing process due to its multiple functions on cellular level[8]. Published clinical data reveal that zinc is also an anti-inflammatory agent.[9] This article explores the possible role of trypsin, bromelain, and rutoside and zinc combination therapy in management of pain, oedema and inflammation.

Methodology

The study was conducted in orthopedic OPD from Jan 2015-March 2015. Middle aged Men and women suffering from osteoarthritis knee were included. Individuals with concurrent medications and disorders, renal impairment were excluded. Individuals with history of hypersensitivity to study drugs were excluded. Ethical committee approval and written informed consent from study subjects was taken prior to the study. The study was designed as randomized, observational and comparative study for a period of 6 weeks. A total of 50 patients with osteoarthritis knee were included in the study, which were divided into two groups of 25 each. One group received diclofenac alone, one tablet b.i.d and the other group received a combination of Trypsin, Bromelain and Rutoside with zinc, two tablets t.i.d; for a period of 6 weeks. Examinations were performed at baseline and at the subsequent visits and at the end of the study with WOMAC index (pain, joint stiffness and joint function).

RESULTS

The results of the study were as follows. Within 6 weeks observation period, the adjusted changes from baseline to endpoint of the target parameters were as follows – WOMAC subscale pain (SET-10.3$\pm$1.2, DC-9.5$\pm$1.2), WOMAC subscale joint stiffness (SET-3.9±0.5, DC-3.6$\pm$0.5), WOMAC subscale physical function (SET -31.7$\pm$3.5, DC -29.7±3.5) with p=0.0025. These results clearly indicate that systemic enzyme therapy is comparably effective as Diclofenac. Systemic enzyme therapy was simultaneously non-inferior as compared to DC with regard to all 4 single endpoints of the study. The tolerability was judged in both drug groups as very good or good, for majority of the patients. The study results concluded that oral enzyme therapy was non-inferior to diclofenac in treatment of patients with osteoarthritis of the knee. The drug tolerability was more in favor of systemic enzyme therapy. The researchers opined that oral enzyme therapy can be recommended for the treatment of patients with osteoarthritis of the knee with signs of inflation as indicated by a high pain level.[10]

DISCUSSION

Pharmacology of Trypsin, Bromelain, Rutoside and Zinc:
Trypsin

Trypsin is a proteolytic enzyme obtained by the activation of trypsinogen extracted from the pancreas of healthy mammals[11]. Trypsin hydrolyzes peptide bonds of the basic amino acids arginine and lysine in proteins as well as esters and amides of a – N- substituted arginine and lysine[12]. Trypsin possesses anti-inflammatory and thrombolytic properties and studies indicate good results in the therapy of thrombophlebitis (both superficial and deep), diabetic cellulitis with chronic infected leg ulcers, rheumatoid arthritis and a variety of ocular disorders[13]. In addition to its role as a digestive enzyme, trypsin has also been shown to exert various cellular effects including endothelium-dependent relaxation and myometrial contraction[14]. There is now substantial evidence that trypsin can regulate target cells by cleaving and activating a growing family of G-protein-coupled protease-activated receptors (PARs).[15]

Bromelain

Bromelain belongs to a group of protein digesting enzymes obtained commercially from the fruit or stem of pineapple. It is a mixture of different thiol endopeptidases and other components like phosphatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors[16]. Bromelain has been shown to have a number of beneficial properties including anti-inflammatory and analgesic actions. Experimental evidence suggests that bromelain's action as an anti-inflammatory is mediated via the following factors: by raising serum fibrinolytic activity, decreasing plasma fibrinogen levels and decreasing bradykinins levels and hence relieves oedema and pain. by decreasing the prostaglandin levels (PGE2 and thromboxane A2) and through modulation of certain surface adhesion molecules.[17] Bromelain is absorbed through the gastrointestinal tract. Bromelain concentration was found highest in the blood after one hour of administration. It is also reported that up to 40% of bromelain is absorbed from the intestine. The half-life of Bromelain after oral administration of 8.6 g each day was 6-9 h and plasma concentration 2.5-4 ng/ml.[18] it is proved that bromelain is well absorbed in body after oral administration and it has no major side effects, even after prolonged use.

Rutoside

Rutoside is a flavonoid richly found in a variety of commonly ingested foods. The name "Rutoside' comes from a plant known as *Ruta gravolents* that also contains rutoside. Buckwheat seeds (*Fagopyrum esculantum)* are the richest source. Rutoside has been reported to have anti-inflammatory and vasoactive properties. Rutoside is an important antioxidant and it has been reported to be a potent scavenger of hydroxyl and superoxide radicals and prevent lipid peroxidation.[19] Published data also indicate that rutoside exhibits multiple pharmacological activities including antibacterial, antitumor, anti-inflammatory, antidiarrheal, antiulcer, antimutagenic, myocardial Protective, vasodilator, and immunomodulator and hepatoprotective activities.[19] Rutoside is incompletely absorbed and extensively metabolized after ingestion. Plasma levels of rutoside decrease rapidly after either intravenous or oral administration. Ingested rutoside is hydrolyzed to quercetin in the intestine and further changed to other conjugated metabolites of quercetin. Rutoside results in the generation of more than 60 metabolities. Many major metabolities, such as quercetin – 3 – glucuronide, possess a 3 -O-glycosidie linkage and are active against Protein Disulfide Isomerase (PDI), as demonstrated by structure activity relationship.[20] it is a safe and inexpensive drug that could reduce clots and thus help save thousands of lives[20].

Zinc

Zinc is the second most abundantly distributed trace element in the body after iron. Zinc catalyzes enzyme activity, contributes to protein structure and regulates gene expression.

The ability of zinc to retard oxidative processes has been recognized for many years. In general, the mechanism of antioxidation can be divided into acute and chronic effects[7]. Wound healing is a complex process involving the stages of inflammation, proliferation and maturation that occur on a continuum from injury to healing. For optimum wound healing these stages must be progressed through smoothly and efficiently, and zinc has an identifiable role in all three stages. The function of zinc in the normal wound-healing process is acknowledged as being evident throughout the inflammatory and proliferative stages.

Zinc is involved in T cell function. It has been reported that Zn-supplying compounds such as polaprezinc and Z-103 suppress autoimmune disease models suggesting that Zn might suppress autoimmune disease by inhibiting T cell activation. However, the details of the mechanism behind this suppression are not understood. Published data reveal that Zn suppresses T helper 17 (Th17) cell development by inhibiting STAT3 (Signal transducers and activators of transcription 3) activation. Peripheral naïve $Cd4^+$ T cell precursor cells can differentiate into three subsets of effector T cells (Th1, Th2, and Th17). The differentiation of these subsets is governed by selective cytokines, and each subset accomplishes specialized functions. Th17 cells, which are critical for the development of inflammation and autoimmune disease, are induced by IL-6 and tumor growth factor beta (TGF-β). Zn directly binds STAT3, inhibiting its activation by IL-6 and suppressing autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen – induced arthritis (CIA) as shown in below figure. Zinc is abundant in bone tissue and is needed to maintain bone mineral density and bone metabolism. Every step of bone metabolism utilizes zinc, and its deficiency is implicated in osteoporosis. The organic matrix of bone is comprised of proteins that require adequate amounts of zinc for optimal function. Zinc acts as a cofactor for osteoblast activity during bone formation and is required for maintaining peak bone density and reducing the risk of age-induced osteopenia or fracture. Recent evidence demonstrates that zinc may act as a local regulator of bone cell formation by stimulating the proliferation and differentiation of osteoblast while at the same time inhibiting osteoclast differentiation. Zinc, thus plays a significant role in bone metabolism and improvement of bone quality. Essential trace minerals such as copper and manganese are required along with zinc for the maintenance of healthy bone tissue[21].

Zinc plays a significant role in bone metabolism and improvement of bone quality

- Zinc has been shown to have a stimulatory effect on osteoblastic bone formation and an inhibitory effect on osteoclastic bone resorption, thereby increasing bone mass. These factors have an effect on protein synthesis and gene expression, which are related to bone formation in osteoblastic cells and bone resorption in osteoclastic cells. Supplemental intake of zinc has been shown to have a preventive effect on osteoporosis in human subjects, suggesting a role in the prevention of bone loss[22].
- Zinc can increase osteogenic effect by stimulating cell proliferation, phosphatase (ALP) activity and collagen synthesis in osteoblastic cells[23].

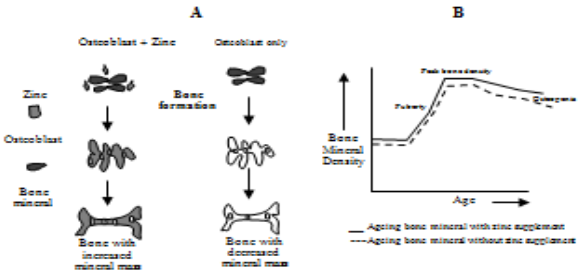

Figure 1 schematic model for the association of zinc with bone mineral density

CONCLUSION

Osteoarthritis is a common painful joint disease, which is effectively treated with NSAIDs, most commonly Diclofenac; but carries the risk of gastric discomfort, gastric and duodenal ulcer and upper GI bleeding. Systemic enzyme therapy is superior in this aspect as they are free from these adverse effects. The combination of Trypsin, Bromelain, Rutoside and zinc is clinically found to be effective in treating conditions like the osteoarthritis of the knee effectively. SET is beneficial in wound healing, reduces spontaneous inflammatory cytokine release and restores T cell functions. Zinc is needed to maintain bone mineral density and bone metabolism. All these factors portray the fact that Trypsin, Bromelain, Rutoside and Zinc may present as an excellent combination in reducing pain, inflammation and oedema in osteoarthritis. Effective therapy can be set forth if rationale combinations of such agents are supported by well-designed clinical trials.

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