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Review Article

Enzyme therapy in sports injuries

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ABSTRACT

Sports and exercise activities are helpful to increase overall health and physical fitness. But also, there is risk of different types of injuries such as sprains, strains, dislocations and fractures collectively known as sports injuries. Sports injuries, if not treated promptly and properly, may lead to lifelong disabilities or may affect athlete's ability to participate in sports. Most of the sports injuries are affecting bones and soft tissues manifesting pain, inflammation and restricted mobility. The common treatment modalities are the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids for pain and inflammation management in sports injuries. But these drugs may lead to severe side effects in long term use. Also, NSAIDs and corticosteroids, do not promote crucial process of remodeling and repair of injury. Hence, there is a need for treatment modalities facilitating fast recovery with less side effects hastening the return to competition by injured athletes. Systemic enzyme therapy (SET) is the enzyme flavonoid combination administered orally and has been recommended since many years for the treatment of pain and inflammation. SET including bromelain, trypsin, rutoside combination has been evaluated and proven effective treatment option for faster recovery with reduced inflammation. These enzymes either in combination or individually show effect on injuries. This review explains types, pathophysiology, current treatment modalities, use of SET and its clinical evidences in sports injury.

Keywords: Proteolytic enzymes, Sprains, Ankle injury, Inflammation

INTRODUCTION

Sports and exercise activities has many health benefits but also there is risk of different types of injuries with different sports and exercises. Also, residual effects of injuries may affect athlete's ability to participate in sports.[1] The term sports injury covers all kinds of injuries that most commonly happen during athletic activities or exercise. There are many possible causes for sports injuries such as Accidents, improper equipment, poor training practices, insufficient warm-up, stretching, lack of conditioning and overuse of a particular body part.[2,3] Sports injuries mostly involves tissues such as ligaments, bones, cartilages, muscles and tendons. Some of the major sports injuries are sprains, strains, dislocations and fractures. Sprain is the condition where, ligaments, which are strong bands of tissues around joints are twisted, stretched or torn. Strains are the result of stretched or torn muscle and tendon. Tendons connect muscles to the bone. In dislocations, a joint is forced out of normal position. Hand, shoulder, elbow, knee and hip joints have chances of being dislocated in sports activities. Bones get broken down due to sudden injury are called fractures. This condition may take time in weeks to heal.

Pain, inflammation, bruising, muscle spasm, loss of strength in muscle and restricted movement are common manifestations of sports injury. Sprains and strains are also known as indirect injury, whereas dislocation and fractures are categorized as direct injury. Overuse injuries is also one of the class of injuries which are mostly a result of repetitive and excessive force on the bones and other connective tissues. Due to asymptomatic early stages and continuation of pressure on the site of overuse

injuries, less healing time given to these injuries. This results into accumulation of damage and further leads to inflammation, e.g., knee and elbow injury.[2,3]

Joints of the extremities such as, knee, hip, elbow, ankle, shoulder and wrist are more prone to sports injuries. Knee injury comprises major part of sports injuries, which is followed by ankle injuries, mostly diagnosed as ligament sprains. Hand and wrist trauma also constitute a part of sports injury. According to a survey in English former professional soccer players, almost half of the players retired due to injury. Also, arthritis is observed as a most common consequence of knee and ankle injuries in athletes. Hence, sports injuries have major impact on athlete's life if, not treated and recovered properly.[1]

SET is a combination of proteolytic enzymes along with flavonoid which has been used since decades due to its therapeutic properties such as anti-inflammatory, analgesic actions, anti-edematous, antioxidant and antithrombotic effects. SET is effective in both, acute and chronic inflammatory conditions and can be used alone or as adjuvant to conventional treatment modalities. SET has been recommended since many years for the treatment of pain and inflammation associated with musculoskeletal disorders, arthritis and post-surgery. In India, different oral formulations of this combination, including enteric-coated tablets (Phlogam®) and dispersible tablets (Disperzyme®) are available. In this review, we are going to understand pathophysiology behind pain and inflammation and their management in sports injuries, role, benefits and clinical evidence of SET in the treatment of sports injuries. [4]

PATHOPHYSIOLOGY

Inflammation is a protective and restorative response to almost every injury. In sports injury, tissues such as ligaments, cartilage, muscles and tendons get injured and leads to pain, swelling, bruises, etc. as an inflammatory response to injury. This process of inflammation involves different types of cells such as platelets, neutrophils, macrophages, fibroblasts and microvascular cells. [5,6]

The process of wound repair and healing can be divided into 3 phases. In phase I, bleeding can be stopped by platelet aggregation and vasoconstriction of blood vessels. At the site of injury, increased blood flow and transport of cells initiates healing. Also, at the site of injury, removal of damaged cells and putting new collagen helps in healing. Platelets release inflammatory mediator bradykinin. Platelet-derived growth factor (PDGF) and transforming growth factors A1 and 2 (TGF-A1 and TGF-2), which act as chemoattractants, are also the response to platelet release. In phase II, new collagen fibers start forming a scar. In this phase, various inflammatory cells release a variety of mediators and cytokines to promote thrombosis, angiogenesis and re-epithelialization. The cells also release proteases that clear the wound of foreign bodies and debris and reactive oxygen species (ROS) that are antimicrobial. Migration of epidermal and dermal cells for the formation of granulation tissue and release of growth factors by the inflammatory cells also helps in proliferation. Phase III mainly involves remodeling and maturation of cellular organization. Bonds between collagen fibers are strengthened to improve organization. In this phase, wound achieves maximum strength. Prostaglandins, thromboxanes, leukotrienes and lipoxins are pro-inflammatory agents and play an important role in the inflammatory response. [6]

MANAGEMENT

Pain and inflammation management is the major factor in the treatment of sports injuries. In the management of sports injuries, use of NSAIDs and corticosteroids are the common treatment modalities. The mechanism of action of these drugs is inhibition of inflammatory pathways by interrupting production of inflammatory substances. Orally administered NSAIDs such as aspirin, naproxen and ibuprofen can be available as over-the-counter drug whereas meloxicam and diclofenac are the NSAIDs requiring prescription. For topical (on skin) application NSAIDs also available in the form of gels and patches. Topical NSAIDs act by penetrating into deeper tissues such as joints and muscles through skin and reduces inflammation. Topical form of NSAIDs is applicable for injuries such as strains, sprains and overuse injuries. Though NSAIDs provide relief from pain and inflammation, it's long-term consumption may lead to some side effects such as, GI irritation potentially leading to conditions like GI reflux disease and ulcers, kidney injury and cardiovascular problems. Topical NSAIDs show fewer side effects as compared to oral route of administration.[7,8]

Corticosteroids (steroids) are anti-inflammatory drugs also used to treat acute and chronic sports injury associated with pain and inflammation. There are various routes of administration for corticosteroids such as oral, injection or iontophoresis. Sports medicine physicians, most commonly inject corticosteroids into a joint, bursa, or around a tendon. Prednisone is the most commonly used oral steroid in the treatment of acute back pain and several other acute conditions. Oral corticosteroids have side effects such as high blood sugar, high blood pressure, and emotional changes.[7,8] The administration of corticosteroids may result in necrosis and progressive destruction of the femoral head. The term "drug-induced arthropathy" is used to describe the common pathological lesion.[9]

NSAIDs and corticosteroids helps reducing inflammation and pain, but these medications do not promote crucial process of remodeling and repair of injury. Hence, there is a need for treatment modalities facilitating fast recovery with less side effects hastening the return to competition by injured athletes.

SET

SET is the enzyme flavonoid combination administered orally and has been recommended since many years for the treatment of pain and inflammation. Combination of bioflavonoid Rutin (rutoside) with proteases trypsin and bromelain intervenes different processes such as the modulation of adhesion molecules, the release of inflammatory mediators and the activation of fibrinolysis with consequent improved healing. Bromelain-trypsin-rutoside have beneficial impact on various inflammatory biomarkers including reactive oxygen and reactive nitrogen oxide species (ROS and RNOS), prostaglandins, cyclooxygenase (COX)-related metabolites, cytokines and chemokines, acute phase proteins (e.g., CRP), inflammation-related growth factors and transcription factors (e.g., NF-kappaB) and major immune cell types. [5]

Bromelain is a proteolytic enzyme having anti-inflammatory, antithrombotic, fibrinolytic properties and obtained from pineapple plant, Ananas comosus. Bromelain lowers the symptoms of inflammation by decreasing kininogen and bradykinin levels in the serum by 60%.[10] Bromelain converts plasminogen to plasmin and acts as an effective fibrinolytic agent increasing fibrinolysis.[10,11] Bromelain shows inhibitory effect on platelet aggregation which results in the inhibition of thrombus formation.[12] Bromelain also has antiedematous, antioxidant and proteolytic properties. [13,14] Bromelain acts as an anti-inflammatory agent by influencing prostaglandin (PGE2, PGF2) and thromboxane (B2) synthesis and also by inhibiting T cell signaling and cytokine production. [10,15]

Trypsin is a serine protease which binds with plasmin inhibitors and make available more plasmin for fibrinolysis. This further leads to removal of inflammatory products and adequate supply of oxygen and nutrients improving macro and micro-circulation.[16,17] Accessory molecules on antigen presenting cells can be cleaved selectively by trypsin to increase T cell activation.[18] Trypsin cleaves and activates G-protein-coupled protease-activated receptors (PARs), which play a major role in healing.[19] This leads to Alteration of macrophage surface marker expression and the macrophage secretion profile towards an M2a phenotype which involve in wound healing and fibrosis. [20] Trypsin also lowers the levels of proinflammatory cytokines (such as TNF-α, IL-1, IFN-γ). [21] Trypsin inhibits leukocyte migration as anti-inflammatory effect and also reduces the time of healing by rapid and selective action. [22,23]

Rutin (rutoside) is a natural non-toxic bioflavonoid having anti-inflammatory, antioxidant, anti-diabetic and anticancer activities.[24-26] It has been demonstrated that, rutoside, when added to activated macrophages, inhibits the release of nitric oxide, IL-1, tumor necrosis factor (TNF)-α and IL-6.[24] Rutoside acts as an antioxidant agent by reducing production of iNOS-mediated nitric oxide (NO), hydroxyl radicals, superoxide ion, and lipid peroxy radicals. [27] Bradykinin, histamine, and fibrin degradation products leads to vascular permeability, which can be reduced by rutoside.[28] Hyperpermeability and oedema can also be reduced by rutoside derivative, hydroxyethyl-rutoside. This may lead to improved microcirculation and reduced erythrocyte aggregation.[29] With bromelain, rutoside acts as a supportive agent in platelet aggregation.[30]

CLINICAL EVIDENCES

SET has been evaluated in multiple sports injuries since years and proven effective treatment option for faster recovery with reduced inflammation. Following are some studies conducted to evaluate efficacy and tolerability of SET.

In 1979, Muller-Hepburn, a sports physician, published his experience and success with trypsin bromelain rutoside combination treatment on 45 patients who had sustained sports injuries. In addition to the local application of TBR combination ointment via compresses and iontophoresis, he also administered TBR orally at doses ranging from three coated tablets b.i.d. to ten coated t.i.d. to these patients, some of whom were severely injured, demonstrated a very good therapeutic outcome. A substantial improvement was seen in five of the injured patients. No therapeutic failures were observed by Muller-Hepburn. Very good results were obtained with a regimen of combined oral and local TBR combination after trauma. Even with respect to tolerance, it is superior to conventional therapy with anti-inflammatory agents, the transitional phase between fixation and mobilization is reduced substantially. This permits competitive athletes to resume training earlier and amateurs to return to work sooner.[31]

TBR combination was administered in addition to physical therapy in competitive athletes active in the martial arts in a number of randomized, placebo-controlled, double-blind, comparative studies. Study criteria were size of the hematoma, extent of swelling, spontaneous pain, tenderness and pain on movement, as well as impairment of function and the resulting inability to participate in sports. According to Worschhauser, patients in the TBR combination groups demonstrated a significant improvement in the degree of complaints (study criteria), enabling them to resume participation in the particular sport sooner.

Athletes, from the German national ice hockey league, were examined in a double-blind study during two seasons in order to discover whether the prophylactic administration of TBR combination enabled the injured player to retain his ability to compete more rapidly. Three groups of patients were differentiated. The first group received ten coated tablets of TBR combination t.i.d. following injury. The second group consisted of athletes who had received a protective dose of five coated tablets t.i.d. which was increased to ten tablets t.i.d. following an

actual trauma. In the third group, Worschhauser included all athletes who had been taking a normal dose of TBR combination for a previous injury and had continued the medication because of renewed injury. The evaluation of the average duration of therapy in relation to the administered dose verified that the ability to compete was attained more rapidly with the protective dose. Overall, Worschhauser recognizes enzyme therapy not only as being an effective therapeutic approach, but also as a protective agent with very few side effects for athletic injuries.[32]

Table 1: Summary of clinical trials revealing the effect of proteolytic enzymes on injuries.

Author, year	Study design	Proteolytic enzyme	Indication	No. of subjects	Outcome
Muller-Hepburn, 1979[31]	A study of observed application of oral and local combination of TBR	Trypsin-Bromelain-rutoside combination	Sports injuries	45	Good therapeutic outcome in severely injured patients. Reduced transitional phase between fixation and mobilization.
Worschhauser, 1990[32]	A double-blind study	Trypsin-bromelain-rutoside combination	Sports injury in ice-hockey athletes	Not available	The ability to compete was attained more rapidly with the protective dose of SET
Zollner, 1991[33]	Protective administration of TBR in a randomized, crossed, double-blind study	Trypsin-bromelain-rutoside combination	Prophylactic use in karate fighters	20	Duration of absence due to injury was reduced significantly in individuals at high risk because of a prophylactic dose of TBR combination tablets
Baumuller, 1992[34]	Placebo-controlled study	Trypsin-bromelain-rutoside combination	Sprain ankles	44	Patients treated with SET showed faster recovery with reduced pain and swelling with rapidly restored mobility
Schwinger[34]	Prospective, randomized, parallel group clinical study	Trypsin-bromelain-rutoside combination	Knee or ankle joint injuries in athletes	59	In SET treated group, significant reduction in ankle joint swelling and reduced need of analgesics observed as compared with aesc in treated group
Rathgeber, 1971[35]	A double-blind, placebo-controlled study	Trypsin chymotrypsin	Soft tissue injuries in sport	43	Significant improvement in recovery of bruising, return to function, and fitness to resume play in trypsin chymotrypsin treated group
Masson, 1995[36]	A study of observed applications in general practice	Bromelain	Musculoskeletal blunt injuries	59	Clear reduction in all four parameters tested; swelling, pain at rest and during movement, and tenderness.
Baumuller, 1990[37]	Double blind, placebo-controlled study	Combination of proteolytic enzymes	Sports-related ankle injuries	44	Faster healing and reduction in the time away from training by about 50%.
Lichtman, 1957[38]	Not available	Trypsin (Injection)	Black eyes and bruises in boxers	Not available	Injection of trypsin in the buttocks immediately after injury allowed black eyes and bruises in boxers to subside in one to three days, rather than the usual 10 to 14 days.
Shaw, 1969[39]	Double blind, placebo-controlled study	Combination of proteolytic enzymes	Finger fractures in athletes	71	Significantly improved recovery

Protective administration of TBR combination also verified in a randomized, crossed, double-blind study. Twenty test subjects, including karate fighters with regular fight training and 13 to 21 years of age group were enrolled. This study was divided into two phases, each of which lasted eight weeks. A 14-day medication and training break between the two phases was followed by the cross- over in therapy. Ten test subjects received coated TBR combination tablets in phase 1 and placebo in phase 2. The second group took placebo in phase 1 and TBR combination coated tablets in phase 2. Seventeen injuries were recorded during phase 1 in the first group and 21 in the second group. During the course of phase 2, 20 injuries occurred in the first and 15 in 2nd group. Main criterion for evaluation of protective therapy time of absence from training, work or school. Study shows that duration of absence due to injury reduced significantly in individuals at high risk because of participation in competitive sports after treatment with a prophylactic dose of five coated TBR combination tablets t.i.d.[33]

There are various studies conducted to evaluate the effect of SET on multiple sports injuries. In a study including 56 athletes with typical sports injuries, 38 responded "very well" whereas 8 athletes responded "well" to the SET. Effectiveness and tolerance in SET was evaluated in a double-blind, randomized parallel group study in athletes who sustained soft tissue injuries. In this study, 44 patients were distributed in 2 groups which were either treated with SET or with placebo. Rapid and significant reduction in the hematomas was observed in the SET treated group. This resulted in an early recovery and a return to play for athletes. In one study published in 'The Practitioner', when SET was administered to soccer players, fast recovery was observed in soft tissue injuries such as hematomas and bruises. Also, effusions (blood leakage in body cavity from bruised blood vessels) is reduced in SET treated players. This leads to missing fewer games due to injury. Another study published in 'The practitioner', SET administered to boxers before entering the ring significantly reduced injuries such as, sprains, bruises, cuts and broken vessels. The American boxing association set down that SET should be taken by boxers a few days before the fight to speed up healing and to reduce inflammation caused by trauma. One placebo-controlled study on the most common sports injury, sprained ankles, was conducted with 44 patients. 22 patients treated with SET showed faster recovery with reduced pain and swelling with rapidly restored mobility.[34]

Effectiveness of SET was also evaluated in post-traumatic edema and hematoma in multiple studies. A prospective, randomized, parallel group clinical study was conducted ~~in~~ on 59 patients with knee or ankle joint injuries requiring surgical treatment. Out of these, 29 were treated with SET and 30 with aescin for 10 days. Significant reduction in ankle joint swelling was observed in SET treated group. Also, aescin treated group needed greater amount of analgesics as compared with SET treated group. In another study, SET or placebo given to patients three times daily, five days before surgery. 120 patients divided into 2 groups of 60 patients were treated either with SET or with placebo. Substantial reduction in edema and pain was observed in SET treated group just 3 days after surgery and also, SET treated patients were able to get discharged earlier from hospital due to quick recovery. One more study was conducted on 80 patients who needed to undergo meniscectomy a knee surgery. Half of the subjects received SET and the other half received placebo for 7 days. The symptoms such as pain, edema, swelling, inflammation and limitation of mobility were reduced substantially in SET treated group. It ~~was~~ resulted in earlier knee mobility in SET treated patients. These criteria were also evaluated in 80 knee arthroscopy patients receiving either SET or placebo for 9 days. And the results show~~n~~ effectiveness of SET-in reducing pain, inflammation and increased mobility, leading to faster recovery.[34]

Also, a double-blind, placebo-controlled trial on 43 patients sustaining soft tissue injuries due to accidental trauma in sport was completed to evaluate the effect of trypsin chymotrypsin. Bruising, return to function, and fitness to resume play were the parameters which showed significant improvements in trypsin chymotrypsin treated group. Also, there was considerable reduction in swelling.[35]

CONCLUSION

The known pharmacodynamic properties and various studies referenced from literature, indicate that the combination of proteolytic enzymes and bioflavonoid is an effective alternative to conventional anti-inflammatory drugs like NSAIDs and corticosteroids, in managing pain and swelling following sports injuries. This, when combined with the absence of safety concerns usually attributed to the conventional drugs, make the enzyme-flavonoid combination the preferable option in managing sports injuries.

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