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International Standard Serial Number (ISSN): 2249-6793

International Journal of Universal Pharmacy and Life Sciences 2(3): May-June 2012

INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND LIFE SCIENCES

Life Sciences

Review Article……!!!

Received: 26-05-2012; Revised; Accepted: 30-05-2012

LEECH THERAPY IN KNEE OSTEOARTHRITIS: MECHANISM AND EFFECTS

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Keywords:

Leech therapy, Unani medicine, knee osteoarthritis, anti-inflammatory, bioactive substances

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ABSTRACT

Bloodletting is an ancient therapy and is being practiced in terms of leech therapy as well as cupping with scarification for treating various illnesses. According to Unani classics many diseases are the result of imbalance of body humors and that can be brought in equilibrium by releasing blood. Leech therapy has remained a popular option among Unani physicians for this purpose. *Hirudo medicinalis* has long been used as medicinal leech in European countries, whereas in India, *Hirudinaria granulosa* is used traditionally for therapeutic purposes. Leech therapy is being practiced in knee osteoarthritis very effectively. Recently, several clinical trials have been conducted in knee osteoarthritis that have showed better outcomes with minimal adverse effects. Earlier it was believed that the beneficial effects of leech therapy are merely due to the bloodletting process, whereas, later on scientists are able to discover various bioactive substances in leech saliva. These bioactive substances are injected in to the body tissues during leech bite. It is the bioactive substances which are responsible for these beneficial effects. At present more than 100 bioactive compounds have been isolated that include anticoagulants, antistasins, protease inhibitors, prostaglandins, histamine-like vasodilators, and poorly characterized anesthetic and analgesic compounds. Therefore, the possible mechanism of action of leech therapy in knee osteoarthritis are due to anti-inflammatory, analgesic and anesthetic action, increasing tissue perfusion, relieving oedema and stiffness by reducing venous congestion, facilitating the nutritive and anabolic substances to reach the knee joint by improving blood circulation, increasing the availability of medicaments by its tissue spreading action.

INTRODUCTION

Leech therapy is commonly used since ancient time for various ailments. This is a treatment modality, in which leeches are applied (artificial infestation) to a particular area to treat the diseases. The very first about application of leeches dates back to Ancient Egypt and the data represented by wall paintings[1]; the first written reference was found in a medical poem by Nicander of Colophon (185–135 BC), a Greek poet and physician[2].

In Ancient period, physicians believed that morbid materials accumulated in the blood caused the diseases and by removing those, patients could be brought back to the healthy state. For this purpose, they adopt various bloodletting techniques. Thus, the leech therapy was used to eliminate the morbid material as it gave certain benefits over conventional bloodletting therapy; leeching is slower, less painful; more quantitatively dependable extraction of blood[3].

Avicenna (d. 1037), the great Arabic physician, believed that leeches draw morbid materials very effectively and his Canon of Medicine includes several pages about leech therapy[4]. However, at the beginning of 20th century, scientific evidence began to discredit bloodletting as a therapy for many conditions, and fell out of favor and into disuse[5]. Consequently, leech therapy was disappear from the medical field. Fortunately, this vital treatment modality was able to regain its place in modern medical science especially in plastic surgery, which was done by two Slovenian surgeons (Derganc and Zdravic). They reported in 1960 that they used leeches to help with a procedure in which a flap of tissue was used to close a wound[6]. Since that, leech therapy was prevailed once again and it is currently used for grafted skin flaps, breast reconstruction, digital replants, periorbital hematomas and some other inflammatory conditions.

*Hirudo medicinalis***,** described by Linnaeus in 1758, has long been considered the sole European medicinal leech[7]. It is also a unique species, presently approved for use in medical procedures, such as clearing of pooled blood following certain surgical procedures[8]. In India, *Hirudinaria granulosa* is used traditionally for therapeutic purposes[9]. Besides these, *Macrobdella decora* (American medicinal leech), *Hirudo michaelseni*, *Hirudo nipponia*, *Hirudo verbena*, and *Hirudo orientalis* are also being used for therapeutic purposes[10-13].

Mechanism of action in knee osteoarthritis

Leech therapy is being practiced in knee osteoarthritis very effectively. Leech therapy reduces pain, stiffness, inflammation and joint dysfunction in inflammatory diseases like osteoarthritis of

the knee[14-15]. Recently, several clinical trials were conducted in knee osteoarthritis to evaluate the efficacy of leech therapy. Almost all of them showed positive effects with minimal adverse effects. In a clinical trial, which was carried out by Michalsen, et al., ten patients were treated once with four leeches and six controls were only treated conventionally. They found that treatment with leeches reduced pain significantly after three days and up to four weeks[16]. This study was followed by another trial targeting knee osteoarthritis and found that leech therapy is effective in knee osteoarthritis[17]. In another study, Michalsen and his team mates found that leech therapy helps relieving symptoms in patients with osteoarthritis of the knee. 51 patients with osteoarthritis of the knee were recruited in this study. Leech therapy was given as a single treatment with 4 to 6 locally applied leeches (leech therapy group) to 24 patients (test group), control group (27 patients) was received topical diclofenac therapy for 28-days. Results revealed that 64% of patients with osteoarthritis reported a reduction in pain after treatment as well as functional improvements including restoration of lost mobility for up to three months[18].

In another trial, single-blinded study was undertaken to overcome the placebo effects of the leech therapy in osteoarthritis knee pain. The treatment still provided more significant pain relief in comparison to the control group treated with 'placebo leeches'[19]. Abbas Zaidi, et al., have done a clinical trial to evaluate efficacy of leech therapy in knee osteoarthritis and he found that 'the leech therapy seems to be an effective symptomatic treatment for OA of the knee[20].

Earlier it was thought that the beneficial effect of leeching occur due to its bloodletting process only. Whereas later on scientific researches revealed that the beneficial effects of leeching occurs due to injection of various bioactive substances found in leech saliva[21]. Scientists were able to isolate bioactive compounds including important anticoagulants, antistasins and other protease inhibitors[22]. More than 100 bioactive compounds have been isolated from medicinal leeches[23-24]. Therefore, possible mechanisms of action in knee osteoarthritis are anti inflammatory action of leech's bioactive substances, relieving oedema and stiffness by reducing blood congestion, improving blood circulation, facilitating the nutrition and biological substances to reach the deceased site by its spreading activity and relieving the pain by its anesthetic activity.

The bioactive substances present in leech saliva produce different effects in the host. Proteinase inhibitors are mainly responsible for its anti-inflammatory action in the host, such as bdellins (inhibitors of trypsin, plasmin, and acrosin), tryptase inhibitor, eglins (inhibitors of alpha-

chymotrypsin, subtilisin and chymasin and the granulocyte proteinases elastase and cathepsin G), inhibitor of carboxypeptidase & inhibitor of complement component C1s[23-25]. Eglin c is a potential therapeutic agent for the treatment of diseases associated with inflammation and has been proven effective for the treatment of shock and emphysema in experimental models. Eglin c is well tolerated, with no significant effects on the cardiovascular and central nervous systems, basic metabolism, clotting, fibrinolysis, or complement[26-27]. Gelin likes eglin, inhibits elastase, cathepsin G, and chymotrypsin[28].

The pathology of OA involves the whole joint in a disease process that includes focal and progressive hyaline articular cartilage loss with concomitant changes in the bone underneath the cartilage, including development of marginal outgrowths, osteophytes and increased thickness of the bony envelope (bony sclerosis)[29]. Biomechanical and biochemical forces are involved in cartilage destruction, which is at the core of OA. Excess weight, structural abnormalities, microfractures, loss of joint stability, and joint trauma cause abnormal mechanical stresses on the knee joint[30]. Chondrocytes serve as mechanical stress sensors that trigger elaboration of inflammatory mediators and proteolytic enzymes in response to these abnormal mechanical stresses[31]. Abnormal stresses on the joint and abnormal cartilage, alone or combined, initiate a cascade of proliferative and inflammatory processes that lead to further damage, and a self-perpetuating and progressive cycle of joint disease ensues[30].

The synovium and chondrocytes synthesize numerous growth factors and cytokines due to various mechanical stimuli. These cytokines and growth factors are believed to play a role in the pathophysiology of the disorder. Interleukin (IL) -1 and tumor necrosis factor-β may function to activate enzymes involved in proteolytic digestion of cartilage[32]. IL -1, which exerts transcriptional effects on chondrocytes, stimulating production of proteinases and suppressing cartilage matrix synthesis. Tumor necrosis factor (TNF) may play a similar role to that of IL-1. These cytokines also induce chondrocytes to synthesize prostaglandin E_2, nitric oxide, and bone morphogenic protein 2 (BMP-2), which together have complex effects on matrix synthesis and degradation. Nitric oxide inhibits aggrecan synthesis and enhances proteinase activity, whereas BMP-2 is a potent stimulator of anabolic activity. At early stages in the matrix response to injury and in the healthy response to loading, the net effect of cytokine stimulation may be matrix turnover but, ultimately, excess IL-1 triggers a process of matrix degradation[33]. Hence, it is

believed that the anti inflammatory substances found in leech saliva such as bdellins, tryptase inhibitor, eglins, gelin, inhibitor of carboxypeptidase & inhibitor of complement component C1s, etc. [23-28] inhibit the cytokines and other factors which cause further degeneration.

Hirustasin (Hirudo antistasin) belongs to a class of serine protease[34]. Hirustasin binds specifically to tissue kallikrein[22]. Tissue kallikrein has been identified in joint fluids and in inflammatory infiltrates within synovial membranes. It is suggested that tissue kallikrein and kinins have an important role in synovitis and joint damage[35]. Piguamerin is a serine protease inhibitor of plasma kallikrein and this peptide potently inhibits plasma and tissue kallikrein and trypsin[28]. Therefore, it can be assumed that Hirustatin and Piguamerin protects the joint from further damage by inhibiting tissue kallkrein. When the leech therapy is performed in the knee joint immediate observable action is sucking blood from the site of its attachment. Especially it sucks venous blood which is congested in that area. Thus, by relieving congestion, it reduce the oedema, thus eliminate the pain and other inflammatory mediators and also by relieving congestion it increases the fresh blood supply to that area. According to the basic concept of Unani medicine, many diseases were the result of accumulation of morbid humors and by eliminating these morbid matters, healthy state will be resumed.

Leech therapy increases the blood supply to the affected part by its thrombolytic, anti platelet, anti atherosclerotic action through its various enzymes. In 1950, Fritz Marquardt of Germany isolated a protein from *Hirudo medicinalis* that he named as Hirudin and he demonstrated its thrombin inhibitor effect[36]. Hirudin is used in surgical operations for its anticoagulant property and has been recommended for the prevention of phlebitis and postoperative pulmonary inflammation[15, 37]. Calin blocks collagen induced adhesion and aggregation of platelets[38]. Calin induces an anti-thrombotic effect in a thrombosis model rich in platelets. Besides inhibition of the direct platelet collagen interaction[38], calin also interferes with von-Wille- brand factor collagen binding, which is believed to be one of the initiative events for thrombus formation at sites of damaged endothelium. Interference with this mechanism may provide an antithrombotic potential[39]. Thrombolysis is occurred by destabilase is another important action of leech enzyme. This is performed by the selective hydrolysis of isopeptide bonds of stabilized fibrin. Under intravenous injection, partially purified destabilase preparations exhibited thrombolytic properties, and thrombi formed in the rat were lysed by 75 and 100 percent in 67 and 137 hrs

after intravenous injection of destabilase, respectively[40-41]. Decorsin is a protein isolated from American medicinal leech *Macrobdella decora*. It acts as an antagonist of platelet glycoprotein IIb - IIIa and is a potent inhibitor of platelet aggregation[42]. Antistasin and ghilanten are potent specific inhibitors of the blood coagulation Factor Xa[22]. Leech saliva also contains several other bio-active substances including prostaglandins, apyrase, histamine-like vasodilators, collagenase, piyavit and poorly characterized anaesthetic and analgesic compounds[7, 13, 15, 43]. A pharmacological preparation containing leech salivary gland secretion as an active component was evaluated clinically and found to have a potent arterial antithrombotic effect[43]. Therefore, these bioactive substances provide to maintain access to fresh blood and prevent clotting.

Some bioactive substances like hyaluronidase, which modifies the permeability of connective tissue through various mechanisms[44]. Hyaluronidase is also called as spreading or diffusing substance. It reduces the viscosity and makes the tissues more readily permeable to injected fluids, increasing the speed of absorption[45]. This promotes resorption of excess fluids and extravasated blood in the tissues and increases the effectiveness of local anesthesia. Hence, hyaluronidase from leech saliva helps increase the spread of all salivary secretions[46], thus it clears the path for the active and healing substances to penetrate[37].

Leech saliva also contains poorly characterized anaesthetic and analgesic compounds[7, 13, 15, 43]. Due to these substances, the subject cannot feel the pain of leech bite. This local anesthetic effect to the leech bite lasts for hours or more. It is believed local anesthetic is a polypeptide chain that initially affects the 'A' nerve fibers and the larger 'B' nerve fibers, causes immediate pain relief, and anaesthetizes the leech bite area. There is also a long term anesthetic effect from leech saliva that specially affects the 'C' nerve fibers and the small 'B' nerve fibers that control the sympathetic nervous system. This anesthetic effect can last several months and provide long term relief from sympathetic mediated pain[47].

Leech enzymes also contain some other bioactive substances like acetylcholine, histamine like vasodilators[48]; these substances have dilating effect on the blood vessels and thereby cause the blood to stream to the bite location[37]. Hence, it helps to eliminate morbid materials, inflammatory mediators and increase the availability of healing substances and nutrients to the tissue.

CONCLUSION

Bioactive substances found in leech saliva have several actions such as anticoagulant, vasodilating, pronounced antithrombotic, anti inflammatory, anesthetic, analgesic, thrombolytic actions and increase tissue perfusion. Collectively these actions of leech enzymes found in saliva cause symptomatic relief and improvement in knee osteoarthritis and prevent further damage to the joint. Therefore, leech enzymes relieve inflammation of knee osteoarthritis; relieve oedema and stiffness by reducing blood congestion; facilitate the nutritive and biologically active substances (anabolic substances) to reach the deceased site by improving blood circulation and tissue spreading activity; relieve the pain in knee osteoarthritis by its anesthetic and analgesic actions. Moreover it protects knee joint from further injuries from some inflammatory mediators.

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