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Review Article

A REVIEW OF MAGGOT DEBRIDEMENT THERAPY IN DIABETIC FOOT ULCER

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ABSTRACT

Debridement is the medical removal of dead, damaged or infected tissue to improve the healing process of wound. Debridement is an essential step in the protocol for treating diabetic foot ulcers which occur in at least 15% of patients with diabetes and precede 84% of leg amputations. Debridement may be surgical or non-surgical. Surgical debridement is carried out using sharp instruments. It has some complications like perioperative bleeding and general complications of anaesthesia. It demands skilled surgeon. Non-surgical debridement includes autolytic, enzymatic, mechanical and biological debridement. All the methods have their own advantages and disadvantages. Biological debridement is a technique based on the use of maggots to remove necrotic tissues from chronic wound. Maggots or larvae of flies are applied on the infected wound. Maggots excrete the enzyme which degrade and liquefy necrotic tissue and later on ingest this from the wound. It is relatively painless procedure as compared to the surgical debridement. This technique has been granted FDA approval in US since 2004. All classical and contemporary literature especially PubMed database regarding maggot debridement therapy and diabetic foot ulcer is scrutinised for the review. It was found that Maggot debridement therapy (MDT) is the better technique as compared to other non-surgical debridement methods for management of diabetic foot ulcer. Sushruta the father of surgery was the first to introduce the maggot therapy in context to kaphaja arbuda (a type of tumour). It is the need of time to conserve this basic principle as a non-surgical method for debridement.

Keywords: Larvae, kaphaja arbuda, krumi, makshika

INTRODUCTION

Diabetes is emerging as a new health concern now a day. The lifetime risk for diabetic patients to develop a diabetic foot ulcer (DFU) is 25%. The risk of amputation is increased in these patients with deteriorating outcomes. More than 50% of non-traumatic lower leg amputations are of DFU patients. Up to 70% of diabetic patients with DFU related amputations die within 5 years of their amputations.[1]The standard protocol for DFU management includes – surgical debridement, dressing to facilitate a moist wound environment and exudate control, vascular assessment, control of infection and glycemic control. Even with this comprehensive approach still there is a room for improvement in DFU outcomes. [2] Several adjuvant therapies have been studied to reduce healing time and amputation rate in DFU.

Different clinical and experimental studies have proved that maggot debridement therapy (MDT) is very effective in this regard. Maggot debridement therapy is a biological debridement which is more selective type of debridement. Hence it comes with the benefit of not damaging the healthy tissue in the wound resulting is the decrease in healing period. Moreover, excretion secretion (ES) of maggots contains certain antimicrobial enzymes which proved to be beneficial in severely infected and antibiotic resistant DFU patients.

Medical grade maggots become commercially available in 2004 and today there is a resurgence of interest in MDT with 12 laboratories in 20 countries dispensing them at low cost. Monarch lab in Long Beach, California provides vial containing 250-500 maggots viable long enough for two MDT. [2]

Sushruta, the father of surgery was the first to introduce the maggot therapy in context to tumour. But in the advancement of time, this therapy is vanished from India and also from other countries. In several countries like United State and Europe, MDT is reintroduced and successfully emerging as an effective management in DFU.

This article may serve as a guideline for MDT in DFU, so that this therapy should be reintroduce in India which is the origin place of this therapy.

Review of literature

PubMed database was searched with the keyword ‘maggot therapy’ and ‘diabetic foot ulcer’ to write this review. The search was focused on the articles published from 2009 to 2018 and it was limited to the articles published in English language. Total 15 articles were scrutinized on the basis of relevance. Out of which 4 are retrieved and relevant 11 articles were included for the review. Systemic reviews, Case reports, randomized control trials and experimental studies were included in this review.

Debridement

Debridement includes removal of dead, contaminated tissue from traumatic or infected wound to expose healthy tissue to promote healing. It is a stabilized method in the wound management which results in reduction of infection and improvement in the wound healing. Debridement may be surgical or non- surgical. Non-surgical methods contain mechanical, autolytic, enzymatic and biological debridement. [3]

Surgical debridement [4] -
It is a selective type of debridement where devitalized tissues like slough, necrotic or eschar in the presence of underlying infection is removed by sharp instruments such as scalpel, curette etc. it requires anaesthesia and comes with certain complications like intraoperative bleeding and complications related with anaesthesia. It also demands skilled, trained, qualified and licenced health professional.
Contraindication: intact eschar with no clinical evidence of underlying infection

Mechanical debridement [4] –
It is a non -selective type of debridement. It removes both unhealthy as well as viable tissues from the wound. It is carried out using mechanical force, wet to dry dressings, pulsatile lavage and wound irrigation.
Indications: acute and chronic wound with moderate to large amount of necrotic tissue, regardless of infection
Contraindication: presence of granulation tissue in higher amount than devitalized tissue, inability to control pain, patients having poor perfusion
Complications: it ranges from minor irritation to major bleeding

Autolytic debridement [4] -
It is highly selective method of debridement. It is natural process of debridement by which endogenous phagocytic cells and proteolytic enzymes break down the necrotic tissues. It requires moist environment and functioning immune system.
Indication: non infected wounds, used with other mechanical methods in infected wounds

Enzymatic debridement [4] -
It is a selective method of debridement of necrotic tissues using an exogenous proteolytic enzyme 'collagenase' to debride clostridium bacteria. Collagenase digests the collagen in the necrotic tissue allowing it to detach. It is a relatively slow process of debridement and is not recommended in patients with known sensitivity to product ingredients.
Contraindication: heavily infected wounds, collagenase should not be used in conjunction with silver-based products or with Dakin solution.

Biological debridement [4] -
It is also known as larval therapy or maggot therapy. Larvae of *Lucilia sericata* species of green bottle fly are used for this therapy. The excretion secretion of larvae dissolves necrotic and infected tissues.
Contraindications: abdominal wound contagious with intraperitoneal cavity, pyoderma gangrenosum in patients with immunocompressive therapy

History of MDT [3]

From several historical documents it is evident that maggots were used for wound management since ancient time and known as bio surgeons. The Aboriginals in Australia and Maya tribes in Central America used larvae frequently to clean the wounds. William Baer (1972-1931), the orthopaedic surgeon at the John Hopkins Hospital in Baltimore was the first to use larvae for the treatment of osteomyelitis in children in 1929. Until 1940s American surgeons used MDT. But due to the discovery of Penicillin by Alexander Fleming in 1928 and widespread production and use of this first antibiotic from 1944, this therapy has disappeared. However, only 4 years after the introduction of Penicillin it was found that more than 50% of all Staphylococcus aureus specimen produced beta lactamase, which made them resistant to the mould. Bacterial resistant to Penicillin and other types of antibiotics resulted in failed healing of infected wounds. Hence maggot therapy made their comeback in late 1980s. In the following years, MDT was reintroduced in United State and Europe using maggots of the *Lucilia sericata*.

Evidence of maggot therapy in Sushruta Samhita

Maggot therapy was described in the compendium Sushruta Samhita 1000 BC, under the treatment of tumours. He said that the paste made of nishpava(*Lablab purpureus*), kulattha (*Dolichos biflorus*), pinyaka(a drug made of the left-overs after expelling oil from the seeds of *Sesamum indicum*) with curd cream and lots of flesh is applied on the affected part so that worms and parasites are produced on the ulcer and flies get attracted to it. When a small portion of this tumour is left unconsumed by the worms, it should be cauterized with fire. [5]

How MDT works [6]

Many dipteran species are capable of infesting living vertebrae host. This condition is termed as myiasis. Maggot therapy is performed by experienced medical practitioners under their control. Hence it is a form of artificial myiasis. The flies that cause myiasis are classified in two categories as obligate and facultative parasites. Obligate parasites feed on living tissue hence cause severe damage to healthy tissue. Facultative parasites feed on dead tissue and therefore are taken into consideration for therapeutic use.

Lifecycle of maggots [6]

Around 2000-3000 eggs are laid by adult female *Phaneicia* in a few weeks directly on the food source upon which the larvae can fed. Larvae require moist environment for the development. Hatching of eggs occurs in 18-24 hours depending on optimal conditions. Larvae immediately and actively begin to feed on the source. This vigorous feeding activity is very beneficial as biological debridement of infected wound. Many proteolytic enzymes are secreted by maggots that liquefy the host tissue. This semi digested liquid is a source of nutrients for these maggots. The larvae continue to feed for 4-5 days and grow twice in size to approximately 8-10 mm. After attaining this size, they stop feeding and leave the wound. Now they search for a dry place in the ground where they can pupate. Finally, after metamorphosis an adult fly emerges from pupa.

How to perform MDT

Selection of flies- *Lucilia sericata* and *Lucilia cuprina* which are the green bottle flies are the most commonly used flies for MDT [6]

Preparation for clinical use - Flies are made to lay eggs onto porcine liver and eggs are separated and chemically sterilized. Resultant larvae are sterilized and tested for their microbial status. Larvae are then applied to infected wound under all aseptic conditions.[6]

Application of maggots [3] - There are two methods of application of maggots.

1. Freely crawling maggots are applied to the wound and covered by nylon net. A gauze bandage is kept over it to keep the maggots captured in the wound and let them breath freely. 10 maggots per square cm wound surface are applied for 3 consecutive days. After this period maggots are removed out by washing with saline.
2. Maggots are captured and enclosed in special biobag containing polyvinyl alcohol spaces. The network of biobag is permeable and permits the migration of maggots to the wound. This bag facilitates the application of MDT and also

the inspection of the wound bed during treatment at any time. After 3-4 days, bags are replaced. Physiological saline solution should be used daily to keep the surface wet. Covering gauze bandage should be changed daily to prevent odour and avoid soakage.

Mechanism of action [6]

i) Chemical – maggot secrets a rich soup of digestive enzymes which include carboxypeptidase and serine protease (trypsin and chymotrypsin like enzymes).
   This help in degradation of laminine, fibronectine and collagen type I and II. Hence play a significant role in effective debridement
ii) Mechanical – maggot possesses a pair of mandibles (hooks) which assist with locomotion and attachment with the tissues. These mouth hooks facilitate probing and maceration of wound tissues enhancing the debridement. These hooks also disrupt the membranes which help in penetration of proteolytic enzymes.

Contraindications [3]

1. Open wounds into abdominal cavity due to risk of organ lesions
2. Pyoderma gangrenosum in patients with immunocompressive therapy and septic arthritis
3. Caution should be taken for wounds near large artery and veins.
4. Wounds contaminated with Pseudomonas aeruginosa cause it may have limited effect.
5. Very dry wound because maggots require moist environment.

Clinical studies of MDT

A 74 years old female patient having diabetes for 30 years with foot ulcer reported in surgical clinic department of university Hospital Onofre Lopes (HUOL), university federal do Rio-Grand- do Norte, Brazil in august 2012 was treated with MDT. After 43 days, ulcer surface area was occupied by granulation tissue. It was concluded in this study that MDT is effective and inexpensive method of debridement providing rapid acceleration in process of wound healing. [7]

In a randomized clinical trial in Hawaii, 23 diabetic patients with foot ulcer were treated with MDT for 9 months. In 17 out of these 23 patient's successful outcomes were reported. These 17 patients have shown the complete debridement with formation of robust granulation tissue within their wounds. 6 out of these patients formed granulation tissue even over exposed tendons, thus avoiding tendon excision. While MDT had not closed the patient's wound completely, partial closure of wounds was obtained in all successfully treated patients. 2 of the successfully treated patients required skin graft to achieve full closure and several other demonstrated further closure of their wounds with negative pressure dressings. 1 patient with severe lymphedema had been treated since 2006 without any perceptible closure of his venous stasis ulcer. In 10 days after MDT 75% closure of his ulcer was achieved. Another remarkable feature observed during treatment of diabetic patient with peripheral neuropathy was the return of normal sensation after several MDT. Hence it was concluded that MDT is effective in treatment of complex diabetic wounds.[8]

According to Copenhagen wound healing centre (CWHC) which is a specialized wound healing institution established as a full integrated hospital unit in the socialized government health care system of Denmark, in DFU patients treated with MDT complete debridement was observed after 4 weeks with lower need of amputation. In patients with neuro-ischaemic diabetic foot ulcer it has been demonstrated a shorter time after MDT and significant more antibiotic free days in MDT group.[3]

Experimental studies

Freshly isolated human monocytes were incubated with a range of excretion secretion of maggots for 1 hour and then stimulated with lipopolysaccharides (range 0-100 micro gm. /ml) or lipoteichoic acid (range 0-5 micro gram/ml) for 18 hours. The expression of cell surface molecules, cytokine and chemokine levels in culture supernatants, cell viability, chemo toxins and phagocytosis and killing of Staphylococcus aureus were measured. It was concluded after this experimental study that maggot secretion inhibits the pro inflammatory responses of human monocytes through a cyclic AMP- dependent mechanism. Regulation of the inflammatory processes by maggots contributes the wound healing.[9]

In one study extract of swabs were taken from infected DFU during maggot treatment and observed that, it contains Lusifensins which are the defensins from maggots secreted as a defence mechanism to protect them when they are exposed to highly infectious environment of a wound during MDT. Lucifensins are antimicrobial peptides which act against Gram positive and Gram-negative bacteria. Hence help to reduce infective foci in DFU patients.[10]

In another study, effect of ES from maggots pre-treated with Pseudomonas aeruginosa on the biofilm using micro-titrate plate assay and on bactericidal effect using the colony forming unit (CFU) assay were investigated. The result showed that only 30 micro grams of the ES from pre-treated maggots could prevent and degrade the biofilm of Pseudomonas aeruginosa. However, the CFU count of P. aeruginosa was not decreased when compared to ES from not pre-treated maggots. It is suggestive that ES from pre-treated maggots was more effective than sterile maggot ES against P. aeruginosa.[11]

In other study cDNA libraries were constructed from micro-dissected salivary glands of maggot and whole maggot and they were treated with transposon assisted signal trapping (TAST), a technique for identification of secreted proteins. In this study several putative secreted components of insect immunity were identified including defensins named Lucifensins.[12]

DISCUSSION

Diabetic foot ulcer is the most common cause of lower extremity amputations in more than 50% of non-traumatic amputations with high mortality rate. DFU is always associated with other complications related with diabetes like neuropathy, macro and micro angiopathies and antibiotic resistant due to which these patients are more prone for skin infection with different organisms. Hence integrative approach for the treatment of DFU is the need of time. Debridement is the prime treatment for DFU along with other medications. Surgical debridement has its own complications and limitation, hence non-surgical debridement is many times preferred over surgical debridement. Maggot therapy is one of the methods of non-surgical debridement. Maggot therapy can prove to be a better option as nonsurgical debridement compared with other methods of debridement. Excretion secretion of maggots not only acts as antimicrobial but also regulates the inflammatory process and corrects neuropathy in some extent. This chemical action together with mechanical action is the secret of efficient tissue debridement in diabetic foot ulcer.

Sushruta was the first to advocate maggots on tumour. In other countries also maggot therapy is being used as the adjuvant therapy in wounds and malignancies. Many clinical trials and experimental studies are carried out in different countries which have proved that excretion secretion of maggots contains Lucifensins which are antimicrobial peptides which act against gram positive and gram-negative bacteria and this secretion inhibit the pro inflammatory responses to human tissues. Hence MDT helps improve the complicated wound conditions in DFU. Hence this therapy should be reintroduced in India for DFU management which is the original place of its invention.

CONCLUSION

The potential of maggot therapy in diabetic fool ulcer is proved by many clinical and experimental studies all over the world. Maggots debride wound quickly and effectively without damaging the viable tissues. Maggots are photophobic hence naturally move into the deep crevices which may be beyond the reach of a surgeon's scalpel. Sushruta was the first to invent maggot therapy. Many ancient treatment modalities are disappeared from India in today's era and maggot therapy in of them. It is the need of time to reintroduce this therapy for diabetic wound as there is a lot of evidence showing the effectiveness of this therapy in complex DFU.

Abbreviations: MDT- maggot debridement therapy, DFU- diabetic foot ulcer, ES- excretion secretion

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