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REVIEW

Larva Treatment From Past to Present in Chronic Wounds

Esra Gul[1]* Yashar Nurullazade[1] Ertugrul Kaya[1,2]

[1] Traditional and Complementary Medicine Students Community, Duzce University, Duzce, Turkey
[2] Department of Pharmacology, Medicine Faculty, Duzce University, Duzce, Turkey

*Corresponding Author: Esra Gul, e-mail: egul060199@gmail.com

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Abstract
"Maggot Debridement Therapy" (MDT), known as larval therapy, is one of the traditional and complementary medicine practices with a history of application from ancient times to the present day. It is used in the treatment of chronic wounds that do not heal with conventional treatments. There are many case histories of successful treatment of stubborn wounds such as diabetic foot ulcers with MDT. Since it reduces the need for antibiotics and does not have any known significant side effects, it is an FDA approved treatment method that is now frequently used. In this review study, it is aimed to explain the development steps of MDT from past to present and its application methods and to discuss its medical importance in the light of the literature
Keywords: Larva, Maggot Therapy, Traditional Medicine, Wound, *Lucilia sericata*

INTRODUCTION

Wound is defined as the disruption of the integrity of the skin or mucosa as a result of a trauma. This necrotic condition that occurs in the skin and mucous membranes closes over time with a unique mechanism. This condition is called wound healing and consists of four overlapping physiological stages that usually go smoothly: Homeostasis, inflammation, proliferation and re-maturation. For wounds that do not heal or those that close too late, the removal of tissue debris for various reasons, removal of destructive products such as local infection and/or proteases from the wound bed stops healing [1].

A successful wound healing process depends on effective debridement and infection control [2]. Today, some difficulties are encountered in controlling chronic infected wounds with modern medical (conventional) methods due to the development of resistance to antibiotics and the inability of surgically debriding necrotized scar tissue. In this case, chronic wounds occur.

These kinds of wounds appear as wounds that reduce the quality of human life considerably and also fail to heal by not following the regular healing method, thus increasing the treatment costs considerably [3]. Such situations also require the development of alternative treatment methods or various new treatment methods. "Maggot Debridement Therapy" (MDT), known as larval therapy in some circles, stands out in this sense.

Larvae treatment is the use of sterile larvae of *Lucilia sericata* fly, which is also called green fly among the public, in the treatment of skin wounds to remove dead tissue and inflamed area without damaging the living tissue. Sterile larvae produced in university laboratories or commercial companies are usually applied to the wound by limiting it with cage-style dressings or tea-bag-like structures. With this treatment method, both wound healing takes place and the bad odor caused by necrotic tissue in the cases is significantly reduced [4].

HISTORY OF LARVAE TREATMENT

The history of the therapeutic use of larval therapy (Table 1) to debride necrotic tissue dates back to the beginning of civilization [5]. It was first discovered in the 16th century by the French surgeon Ambroise Pare (1510-1590). Ambroise Pare has tried to treat soldiers' war wounds larvae and achieved successful results. This treatment was first officially documented by John Forney

Zacharias in the American Civil War (1861-1865). It was pushed into the background due to the germ theory developed in the nineteenth century under the leadership of Robert Koch and Louis Pasteur. However, during World War I, when antiseptic devices were not sufficient, it was used by military orthopedist William Baer to treat fractures and wounds and gained popularity again. The first scientific study published on this subject was Prof. Dr. WS Baer who used larvae in the treatment of osteomyelitis in the 1930s. It was used as a standard wound treatment method in chronic infected wounds of soft tissues in hospitals in the United States until the 1940s [4]. After the discovery of antibiotics in the 1940s and the mass production of sulfonamides and penicillin, the use of larvae became limited to stubborn wounds and was out of use for a while Sherman, who conducted one of the oldest (1988) rewiew studies on this subject, used larvae for the treatment of chronic osteomyelitis and reported that antibiotics were ineffective in this treatment and that it was suitable for situations where surgery was not possible [7]. Larva Treatment has come to the fore again with the development of the sterilization methods required for larva treatment with the advancing technology towards the 2000s and the antibiotic resistance problem in bacteria [8].

NEXT TERM STUDIES

Larval therapy was first implemented in 2002, and the treatment of difficult healing wounds with the larvae of Lucilia Sericata in 2007 in Turkey "project is supported by TUBITAK [9]. In the same year, a study was published stating that larval treatment is the first choice in leg ulcers, carbuncles, pressure ulcers and infected traumatic wounds, and its beneficial effects are also seen in eliminating the diabetic foot and malignant tissue [10]. Whitaker et al. (2007) stated that the clinical indications for larvae treatment are diverse, but the main indication is the presence of major comorbidities that prevent surgery and wounds infected with multidrug-resistant bacteria [5].

Falch et al.'s study in 2009 showed that larvae debride wounds by dissolving necrotic tissue, show an antimicrobial effect and support wound healing [11]. In different studies, it has been reported that the larvae provide faster wound granulation [2, 12-14]. Bolaban (2009) studied samples from 23 identified diabetic ulcers and 2 chronic wounds and concluded that larval secretions reduced colonization of MRSA (methicillin resistant *Staphylococcus*), MSSA (methicillin susceptible *Staphylococcus*) and *P. aeruginosa* by 50% [15] Nenoff et al. (2010) used MRSA strains in their study and showed that the larvae have antimicrobial activity against gram-positive bacteria as well as necrectomy and debridement properties [12]. It has been shown in studies that the secretions of the larvae contain allantoin, cysteine, sulfhydryl radicals, glutathione, ammonia, calcium carbonate and growth stimulating factors. It has also been reported that the larvae have many digestive enzymes, including carboxypeptidase A and B, leukine aminopeptidase, collagenase, and serine proteases (trypsin-like and chymotrypsin-like enzymes) while feeding on the wound, thus showing a successful debridement [15-18].

Zarchi et al. (2012) showed three randomized clinical studies and five non-randomized studies evaluating the efficacy of sterile *Lucilia Sericata* applied to ulcers of various etiologies in their systematic study. As a result, it has been reported that there is a significant difference in debridement and recovery in larval treatment compared to conventional treatment such as saline moistened gauze [18]. The treatment of larvae was not only evaluated in terms of its effectiveness and mechanism, but was also examined in terms of its side effects and it was observed that the larvae could sometimes cause an itching sensation, and some patients needed analgesic due to the pain they cause during larva treatment [14].

LARVA TREATMENT APPLICATION METHODS

The method of administration is as important as the effectiveness of larval treatment. A lot of research has been conducted on the application of the treatment, the type of larva used and its production. Historically, *L. sericata* and *L. cuprina* larvae are considered to be beneficial in the treatment of ulcers. Recently, larvae of various other fly species

(*Calliphora vicina, Calliphora vomitoria, Phormia regina, Chrysomya albiceps, Sarcophaga carnaria and Hermetia illucens*) have been shown in vitro to have characteristics that make them favorable (i.e. debridement efficiency and putative antimicrobial potentials). The larvae generally do not damage the healthy dermis and subcutaneous tissue; However, the risk of damaging the healthy epithelium should not be forgotten [3,5,13].

There are two different application methods of Larva Treatment, mainly the Cage method and the Biobag. In the cage method, adhesive hydrocolloid materials are cut according to the wound and the edges are framed with this material so that the wound is exposed. A sterile piece of fine gauze is cut wider than the wound and smaller than the hydrocolloid frame. This tulle is attached to the hydrocolloid frame with adhesive tapes with one end exposed. After the larvae are left to the wound from the exposed end of the tulle, this part is also closed. Sterile tampons are placed on the tulle to ensure drainage. Tulle allows larvae to breathe as well as facilitates the drainage of necrosis tissue [19].

In the biobag method, the larvae are placed between two pieces of tulle made of 0.5 mm thick special material (polyvinylalcohol-hydro-sponge) as in a tea bag and the mouth of the bag is glued. Because the bags are permeable, the larvae can be fed and their secretions penetrate the wound so that infection control and recovery can be achieved. In this method, a cage-style dressing is not needed. After the bags are placed directly on the wound site, they are wrapped with gauze or a bandage in order to remain fixed [19].

There are studies to find out which of these two methods provide more effective wound debridement and how well the larvae can affect the wound with these methods-comparing the advantages and disadvantages. Accordingly, it has been reported that the development of the most appropriate and effective original package designs containing sterile larvae is important for practicality in practice and successful treatment [20]. This method called "biobag" is thought to have advantages such as preventing mechanical irritation due to the larvae walking directly on the wound and reducing pain due to this [19,21].

Disinfection of larvae to be used in treatment is also one of the important points during the application. If it is applied improperly and necessary precautions are not taken, septicemia may develop[22]. For this purpose, 20% sugar solution is given to the larvae to be used in the treatment. Pieces of meat or liver are used to stimulate ovulation. After that the collected eggs are separated from each other and their surfaces are disinfected with 1% sodium sulfite solution added to physiological saline with 2.5% formaldehyde, using a mixture of 3% Bakto Agar and crushed liver (1:1 weight/volume) is transferred to the prepared sterile medium. Approximately 2-36 hours later, the larvae hatched from the eggs are removed from the fattening place and placed in sterile containers for use in treatment. Sterile larvae can live for up to five days without losing their vitality at 5-8 ºC [4]. Studies on the production of the larvae to be used and the supply chain management have lagged behind the investigation of the effectiveness of larval treatment [23].

CURRENT STUDIES AND LATEST STATUS

Larva treatment, which started as a last-resort trial in aggressive chronic wounds and has historically become one of the traditional methods, is now an FDA-approved therapy against MDT, non-healing skin and soft tissue wounds [1]. Given its ability to reach necrotic areas, prevent unnecessary living tissue debridement and only debride dead tissue, accelerate wound healing, antibacterial effects and no side effects, it is an appropriate method in the treatment of pressure sores in patients with MDT resistant, with both cheap and fast and effective recovery [23]. It is widely used in treatment all over the world. Zurairie et al. (2020), with a more comprehensive study involving 580 patients, concluded that larval treatment provides a faster and more effective debridement than conventional treatment, and leads to a faster development of granulation tissue [24] be carried out in Turkey in 2014 by the Traditional and Complementary Medicine Practices regulations and other doctors treating larvae with the traditional treatment has been made official. Özkan et al. (2019) states that

in addition to the treatment of bacterial-induced ulcers, it can also be used for symptoms associated with mycotic infection and leishmaniasis [1].

Many studies have been conducted on which types of wounds the Larva Treatment, which is such an effective method of debridement, can be used in which ones, and many cases have been presented. Four cases concerning the use of maggot therapy in Turkey are listed below;

In case one, on the 45th day of hospitalization, stage 3 pressure sores of the patient developed 7 cm in the sacrum area, 8 cm in the right trochanter and 3 cm in the left trochanter, and the wounds of the patient were resistant to conventional treatment and did not heal. Because of the presence of dense necrotic tissue and infected areas in the pressure wound, the patient was not able to undergo surgical debridement. The larvae were placed with the cage method for 3 days and replaced with new larvae at the end of 3 days and the dressing was changed 4 times a day as they got dirty during this period. Maggot debridement treatment was continued for a total of eight days and MDT was discontinued at the end of the eighth day. As a result of MDT, it was observed that necrotic tissues disappear completely [25]. In case two, a seventy-five-year-old female patient with chronic venous insufficiency for 10 years was treated with different methods for 11 months for 11 months of the infection in the second toe of the right toe, which was ulcerated one year ago and was amputated due to no response. Considering the risk of amputation of other fingers, it was decided to start maggot therapy. Maggot was applied once a day for 3 days, a response was obtained in 3 days, and then autologous skin transplantation was performed on it and complete treatment was achieved. During the application of maggots, the patient did not have any major complaints, except for an increase in pain, which was eliminated by giving analgesics. In conclusion, in patients with chronic cutaneous ulcer who do not respond to conventional treatment methods, maggot debridement treatment is seen as an alternative treatment option that is economical, easy to apply, gives quick results and has few side effects [26]. In the third case report, a 33-year-old male patient with spinal cord injury (SCI) developed a 3*2cm stage 3 pressure sore on the postoperative 2nd day. Although the patient received convectional wound therapy for 3 months, she did not recover and resistance to treatment developed. Mechanical and surgical debridement could not be achieved because of the presence of necrotic and infected areas and preservation of pain sensation; Larvae treatment is planned. Larvae treatment was applied by changing the larvae once every 3 days in cycles of 48-72 hours with the cage method in a way that the 1-2 day-old larvae were 5-10 larvae per cm^2. The tulle on the cage was also changed every 6-8 hours. In this way, it was seen that the wound was completely closed on the 3rd week [27]. In the fourth case report, a 60-year-old 14-year-old DM patient was administered conventional wound care and antibiotic prophylaxis for 6 years due to grade 2 diabetic foot wound in the right foot Achilles tendon area. During the process, the wound got bigger and infected due to circulatory disorders. Two years ago, a left leg below the knee amputation was performed due to a diabetic foot wound. MDT was recommended for the treatment of necrotic tissues before any surgical intervention was planned for the patient who had two strokes and 1 heart attack. MDT was applied to our patient with 2 sessions of cage dressing for 5 days. Since the pain of the patient reached an unbearable level in the first session, the treatment had to be stopped at the 48th hour. In the second session, conventional TENS was applied to reduce the pain that would occur in the patient and the treatment was continued for 72 hours. At the end of 5 days, it was observed that sufficient wound debridement was achieved and the treatment was terminated [28].

In addition to all these, larval treatment, which has a wide area of use in chronic wound treatment, has found application in veterinary medicine. Although its use and studies in animals are very few, successful results have been obtained in a limited number of studies [29]. Studies have also reported that larval treatment on animals has been largely successful in wound healing [19].

Table 1. Chronological order of studies on larval treatment

No	History of The Study	Name of The Study	Author of The Study	Wound-Regıon Worked On	Result
1	1931	The treatment of chronic osteomyelitis with the maggot	Baer[6]	chronic osteomyelitis	Recovery was achieved in almost all patients.
2	1988	Maggot therapy: a review of the therapeutic applications of fly larvae in human medicine, especially for treating osteomyelitis	Sherman et al.[7]	chronic osteomyelitis	It continues to be suitable for situations where antibiotics are ineffective and surgery is not feasible.
3	2001	Clinical applications for maggots in wound care	Mumcuoğlu[14]	Necrosis wound	It is a simple, efficient, well tolerated and cost effective tool in the treatment of wounds and ulcers that do not respond to conventional therapy and surgical intervention.
4	2002	The effect of containment on the properties of sterile maggots	Thomas et al.[21]	Research has been done on the properties of sterile maggots.	showed that free-range maggots survive and grow significantly faster than maggots in the bag
5	2002	Clustering of bloodstream infections during maggot debridement therapy using contaminated larvae of Protophormia terraenovae	Nuesch et al.[22]	chronic ulcer	Application on chronic ulcers seems safe, provided the maggots have been effectively disinfected.
6	2006	Maggot Therapy: The Science and Implication for CAM Part I – History and Bacterial Resistance	Nigam et al.[8]	Necrotic tissue	Maggot therapy can be used successfully in the treatment of chronic, long-term, infected wounds that previously failed to respond to conventional therapy.
7	2007	Treatment of a chronic venous ulcer patient with maggot debridement treatment	Özkan et al.[26]	chronic ulcer	With maggot therapy, it was determined that the ulcer was completely cleared from necrotic and suppurative tissue.
8	2007	Larval therapy from antiquity to the present day: mechanisms of action, clinical applications and future potential	Whitaker et al.[5]	The history of larval therapy has been studied.	The use of larval treatment application is increasing all over the world due to its effectiveness, safety and simplicity.
9	2007	Maggots of *Lucilia Sericata* in treatment of intractable wounds	Orkiszewski[10]	Today, the treatment of maggots has turned into less treatment as a last resort, but it is the first choice for leg ulcers, carbuncules, pressure ulcers and infected traumatic wounds.	Clinical experience has shown that maggot treatment can significantly reduce treatment costs by shortening hospital stay and reducing the use of antibiotics.
10	2008	A review of the use of maggots in wound therapy	Gupta[3]	Chronic wound	The use of larval therapy on chronic wound has been studied.
11	2009	Maggot Debridement Treatment of Suppurative Chronic Wounds	Mumcuoğlu[4]	Suppurative Chronic Wound	Cleaning and granulation of MDT in chronic wounds proven to be an effective method of startup.
12	2009	Maggot therapy in wound management	Falch et al.[11]	Chronic wound	-
13	2009	*Investigation of Antibacterial Effects of Lucilia Sericata Larvae and Secretions on Methicillin Resistant Staphylococcus Aureus (MRSA) and Methicillin Sensitive Staphylococcus Aureus (MSSA) Under In-Vivo and In-Vitro Conditions*	Bolaban[15]	In vitro experiment	In in-vitro experiments conducted in our study, it was observed that larval secretions decreased the number of MRSA, MSSA and P. aeruginosa colonies by 50%.. In our study Lucilia sericata on various lethal microorganisms and enzyme secretions of the larvae and reproductive effects stopper has been demonstrated for the first time in Turkey.
14	2009	Maggot Therapy Application in Conventional Therapy Resistant Sacral Compression Wound: A Case Report	Tuğcu et al.[27]	Pressure sores	There was a dramatic improvement in the patient.

15	2010	Biosurgical débridement using *Lucilia Sericata*-maggots-an update	Nenoff et al.[12]	chronic ulcers that don't heal	Chronic wound debridement, reduced bacterial load, and improved wound granulation.
16	2010	Larval Debridement Treatment	Polat et al.[9]	Foot wound	The wound is completely healed.
17	2012	The efficacy of maggot debridement therapy--a review of comparative clinical trials	Zarchi et al.[18]	3 randomized clinical trials and 5 nonrandomized trials applied to ulcers of various etiology were shown	7 studies had debridement and / or recovery as outcome variables
18	2013	Multiple actions of *Lucilia Sericata* larvae in hard-to-heal wounds: larval secretions contain molecules that accelerate wound healing, reduce chronic inflammation and inhibit bacterial infection	Cazander et al.[16]	Up-to-date information on wound healing mechanism has been compiled.	Molecules involved in wound healing may be candidates for the development of new agents.
19	2014	Sterile *Lucilia Sericata l*arvae in the treatment of chronic wounds uygulamaları.	Tanyüksel et al.[20]	23 diabetic ulcers, 2 chronic wounds	19 full cure, 6 partial debride
20	2015	Maggot Debridement Treatment in Pressure Sore: A Case Report	Yağız et al.[25]	Stage 3 pressure sores	necrotic tissues disappeared completely
21	2016	Maggot debridement therapy as primary tool to treat chronic wound of animals	Choudhary et al.[29]	Limb wounds in animals	A very safe, efficient and easy healing method for chronic wounds.
22	2016	TIME management by medicinal larvae	Pritchard et al.[17]	Venous leg ulcer	Debridement is provided.
23	2017	The Use of Myase Fly Larvae in Wound Treatment	Yaman et al.[19]	Information was given about the history of larvae, method of use, number, indication contraindication, wound healing mechanism..	In recent years, successful results have been obtained by applying maggot therapy to a large number of patients. In the future, maggot therapy may be replaced by larval-derived drugs.
24	2017	Larval Therapy for Chronic Cutaneous Ulcers: Historical Review and Future Perspectives	Raposio et al.[13]	Chronic cutaneous ulcer	It accelerates the wound healing process.
25	2018	Painless approach to maggot debridement treatment in a diabetic foot ulcer patient: a case report	Uçar et al[28]	Stage 2 diabetic foot	Adequate debridement provided
26	2019	Larval Therapy and Chronic Wounds	Gazi et al.[1]	Pressure sores	Debridement is provided.
27	2019	Effectiveness of Chronic Wound Debridement with the Use of Larvae of *Lucilia Sericata*	Bazalinski et al.[2]	Venous ulcer	The wound was treated more cost-effectively.
28	2020	The maggot therapy supply chain: a review of the literature and practice	Stadler[23]	Researching supply chain management through the conceptual and disciplinary framework	There is not enough work.
29	2020	Maggot Therapy in Wound Healing: A Systematic Review	Zubir et al.[24]	The full text of five studies involving 580 patients with chronic wounds was included.	It provided faster and more effective debridement of necrosis tissue.

CONCLUSION

Larvae treatment is an easily applicable and successful method in traditional and complementary medicine. Although it has been discredited from time to time in the historical process, it has become a widely used FDA-approved form of treatment today. The fact that it has almost no side effects, reduced the need for antibiotics and the successful results of the studies

made larval treatment an important reason for preference in chronic wound treatment. It is interesting to see success with MDT in chronic wound treatment, especially in cases where conventional treatment has not been successful. The microdebridement ability and proteolytic enzymes of the larvae appear to be key to this success. Larva treatment in the coming period; It seems that it will continue to be a hope for many desperate patients with its current scientific evidence and application practice and will find a place in conventional medicine applications beyond the field of traditional medicine.

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