Tamap Journal of Engineering
http://www.tamap.org/
doi:10.29371/2019.3.103
Volume 2019, Article ID 103
Research Article

Diabetic Pressure Ulcer Treatment Methods and Maggot Therapy-Review

Duygu ÜNER-BAHAR[1,*] and İbrahim IŞILDAK[2]

[1]*İstanbul Gelişim University, Vocational School of Health Services, Biomedical Device Technology, İstanbul, Turkey*

[2]*Yıldız Technical University, Faculty of Chemical and Metallurgical Engineering, Bioengineering Department, Istanbul, Turkey*

Received: 02.12.2019 • **Accepted**: 30.12.2019 • **Published Online:** 31.12.2019

Abstract: Pressure ulcers are areas of regional tissue necrosis that develop as a result of long-term pressure on soft tissue between the bone structure and the outer surface [1], [2], [3]. The most common areas for pressure ulcers are the skin surfaces on the bone protrusions, sacrum, tuber ischiadicum, trochanter major, heels and lateral malleols [4]. Pressure sores are important health problems that cause an increase in health care institution costs, an increase in the amount of care allocated to the patient, a negative psychosocial effect on the patient, a prolonged hospital stay and a negative impact on the economy of the country. Approximately 18% of hospitalized patients are thought to have pressure ulcers [5]. While 10% of pressure sores occur in mobilized patients, 53% develop in bed-care patients and 37% develop in wheelchair users [6].

The cost of pressure wound treatment per patient was between $20,900 and $151,700 in 2011, with an annual cost of around $11 billion in the USA [7], [8]. Between 2003 and 2008, pressure ulcers were the direct cause of death for 4708 people in the UK, with an average cost of care of £2 billion [9], [10]. Every year, 2.5 million people are diagnosed with pressure ulcer wounds in Turkey. The cost of pressure ulcer sores in Turkey is calculated to be $11.5 billion in 2011 (Turquoise Standards). These costs are made with special calculation engines [11]. Considering the cost of medication, antibiotherapy, surgical intervention, a bed, a room, physician consultation, nursing care, and laboratory expenses, it is of great importance to rapidly and economically improve and prevent such wounds that adversely affect both patients and the state economy.

In this study, the stages of compression ulcers are examined and current treatment methods are summarized. The advantages and disadvantages of maggot therapy, which is a very effective treatment method in the treatment of pressure ulcers, were evaluated and information was given regarding the wound dressing loaded with maggot larvae, which provides a more economical and simple treatment against pressure ulcers developed by the author and his team.

***Keywords**:* Pressure ulcer, diabetic ulcer, wound therapy, public health, quality of life.

1. INTRODUCTION

Pressure ulcer (decubitus ulcer) refers to skin or tissue damage due to decreased blood circulation, due to constant pressure on a particular area. Pressure, friction, moisture, and stress are the factors that cause pressure ulcers in general.

* Correspondence: duner@gelisim.edu.tr

It is one of the important problems that may occur in patients who are bedridden for long or short periods. It is very common especially in patients with a history involving strokes. Treatment of these wounds, due to a complex process of tissue destruction, requires a multidisciplinary approach and is costly to treat [2].

Pressure ulcers were classified internationally (1989 in the National Pressure Ulcer Advisory Panel (NPUAP) 1989) to achieve a more effective treatment [3], [12]:

• Stage I: Non-whitening erythema of intact skin. There is redness on the skin that does not fade by suppression. However, skin integrity is preserved.

• Stage II: Skin loss of thickness affecting the dermis or epidermis. Abrasion can be seen as a narrow crater or crack. There is a superficial loss.

• Stage III: Full-thickness skin loss, including subcutaneous tissues. It may extend to the lower fascia but does not contain it.

• Stage IV: Full-thickness skin loss, deeper. The underlying muscle or bone and joint capsule are also affected. Sinus tract may be present. There was severe tissue loss [1].

Figure 1 shows the developmental stages of compression ulcers [13] and an example of sacral region pressure ulcers.

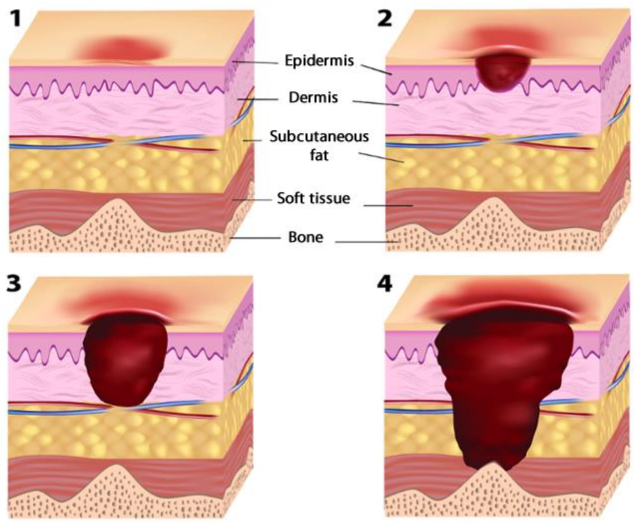

Figure 1. Press ulcer development stages [3] and sacral region pressure ulcer sample *(shared with patient permission)*

Effective parameters in the development of pressure ulcers; pressure, stress, friction and moist environment. Normal capillary pressure is 32 mmHg in arterioles and 12 mmHg in venules [14]. Pressures above 32 mmHg cause an increase in interstitial pressure, disrupting oxygenation and microcirculation. A pressure above 70 mmHg, which lasts more than two hours, causes tissue death [1]. The areas most exposed to pressure are the soft tissue regions above the bone protrusions [2]. In a 1959 study of dogs, irreversible tissue damage was observed as a result of a pressure of 70 mmHg applied for 2 hours [15]. Prolonged exposure to low-pressure or short-term high-pressure can lead to similar tissue damage [16], [17]. If the head of a patient lying in a supine position is raised more than 30 °, the wounds occur especially in the sacral and coccygeal regions [1]. Friction in pressure ulcers accelerates the process by reducing the amount of pressure required for wound formation. Also, prolonged exposure to a moist environment facilitates superficial skin destruction.

Pressure ulcers can cause various infections. The skin has normal flora, though. A distinction is needed between bacterial colonization and bacterial infection. 106 types of bacteria in tissue flora are considered to delay wound healing [18], [19]. If bacteremia develops, it may result in sepsis, endocarditis, and even death. These complications are more common in the presence of diabetes mellitus.

Staph. aureus, Staph. epidermidis, Strep. Group A, E. coli, Pseudomonas aeruginosa, Proteus mirabilis, Serratia marcescens, Enterobacter spp. and Acinetobacter spp. are known to be isolated from wounds [2]. The causative agent of sepsis is polymicrobial. Osteomyelitis may develop by direct spread or hematogenous pathway and is found in approximately 26% of non-healing ulcers [20].

2. Methods Applied in Pressure Ulcer Treatment

Stage I-II-III compression sores can be treated to a large extent with local wound care if the patient does not have additional diseases. Local wound care consists of the following steps [1], [12]:

1- Reducing the pressure,
2- Reducing bacterial content,
3- Removal of necrotic tissues,
4- Providing a moist environment,
5- Diagnosis and treatment of infection,
6- Filling the dead space

In the treatment of chronic wounds that cannot be healed by local care, adjunctive treatment methods, surgical closure of wounds and the use of hydrocolloid dressings may be preferred.

2.1. Auxiliary Treatment Methods

There are many adjunctive methods in the treatment of chronic wounds resistant to local care. These can be listed as follows [21]:

1. Hyperbaric Oxygen Therapy (HBO)
2. VAC Treatment (Vacuum-Assisted Closure)
3. Larval Therapy (Maggot Therapy)
4. Intermittent positive pressure devices
5. Electrical stimulation
6. Cell Origin Wound Healing Technologies
7. Stem Cell Therapy - Growth factor

1. Hyperbaric Oxygen Therapy (HBO): This treatment method is based on 100% oxygen inhalation by putting the patient under pressure in the pressure chamber. Treatment can be administered between 1-3 ATAs and for different periods depending on the patient’s disease [22], [63].

2. Negative Pressure Wound Treatment (VAC-vacuum assisted closure): Sterile closure of the wound area is ensured and negative or continuous pressure is applied to the wound area. Thus, local blood flow is increased, local edema is reduced, granulation tissue development is accelerated, bacterial colonization is reduced, infection is contracted, moist wound environment is provided, epithelization is accelerated and wound contraction is achieved. This method is generally used in chronic wounds, diabetic foot wounds, pressure ulcers, venous ulcers, acute and traumatic wounds, and nonunions.

3. Larvae (Maggot) Treatment: In this treatment method, green fly (Lucilia sericata) larvae are used for treatment. Maggot therapy is a treatment modality with no side effects in late-healing or non-healing (chronic) wounds where wound debridement cannot be performed adequately for various reasons. Larvae provide wound debridement by eating

bacteria and dead tissues. Granulation tissue development in the wound is thus accelerated. On the other hand, larvae are thought to increase the efficacy of growth factors in the wound area with some secretions [23]. There are also some considerations in the use of larvae. Due to the difficulty in obtaining and sterilizing larvae, the use of this method has been reduced after the 1950s with the development of conventional dressing materials. However, maggot therapy could be the preferred method in non-healing wounds resistant to conventional dressings. The most important drawback in Maggot Therapy is the use of non-sterile larvae. It is important to produce them in a reliable center and to quickly destroy the larvae used. Theoretically, the larvae 'enzymes can cause allergies, but no such instance has been reported [21].

4. Intermittent positive pressure application: Foot, knee or whole leg can be applied with pressure to reduce edema. Blood circulation can be adjusted to regulate the pressure and duration of a method. The pressure is applied to the leg with the aid of a wearable tool. It is especially useful in venous ulcers. It can be used in all wounds where the negative effect of edema is seen.

5. Electric Stimulation (Electromagnetic Therapy): It is a form of treatment involving the application of electric current to the wound area or by creating a magnetic field in the wound area. It has a positive effect on granulation tissue development, collagen matrix formation, neovascularization development, and epithelialization.

6. Cell Origin Wound Healing Technologies: Other grafts may cause different risks to wounds. For example, autogenous and non-autogenous skin grafts can produce a wound site with immune rejection, infection transmission and various risks (pain, infection, delayed healing, etc.). Therefore, biocompatible wound dressing materials, which are non-antigenic, ready for transplantation, which provides histological and functional characteristics of human skin, can be used immediately and have been developed by tissue engineering and stem cell studies. There are many products developed in this context: cultured autologous keratinocyte grafts, cultured allogeneic keratinocyte grafts, autologous/allogeneic composites, acellular collagen matrices, cellular matrices, etc. Many of these are still under development and testing [22].

7. Stem Cell Treatment: Immediately after a skin injury, mesenchymal stem cells taken from bone marrow adapt to the peripheral circulation and surround the skin adnexa, and eventually turn into skin cells. In patients with autologous culture and bone-derived mesenchymal stem cells transplanted, in human cases, rapid granulation development and healing were observed in chronic wounds [22]. Growth factors, platelet-derived products, laser, shock waves, ultrasound applications, and many extracellular matrix products are commercially available [21].

2.2. Surgical Closure of Pressure Sores

When selecting the surgical method to be applied, evaluation should be made according to both the patient and the ulcer. The main purpose of surgical closure methods is to ensure that sufficiently intact tissue can be transported to the ulcer site. The points to be considered while planning is to close the wound without leaving any gaps and to ensure that no tension is applied to the sutures regardless of the position given to the patient. Methods and materials that can be used for this purpose are primary closure, skin grafts, local skin flaps, muscle and muscle-skin flaps, fasciocutaneous flaps and neurosensory flaps. Because primary closure and skin grafts require high repetition, they are only applied to patients who are expected to stand up in the future. Small skin flaps prepared from the adjacent skin to the ulcer site usually fail. They use muscle-skin flaps especially in the treatment of infected wounds involving deep cavities [23], [24]. In this way, well-blooded muscle tissue is transported to the infected site and applied systemic antibiotics are enabled to work. The fasciocutaneous flaps also have adequate blood circulation and are highly resistant to ischemia, thus forming a firm covering. Another method is to close the sensory innervation of pressure sores with neurosensory flaps that take the levels above the spinal cord injury. These methods, which have theoretically significant advantages, could not find much application in the clinic due to their technical difficulties.

2.3. Use of Hydrocolloid Wound Dressings in Treatment of Pressure Wounds

Hydrocolloid materials are widely used in the treatment of pressure ulcers [25]. Hydrocolloid dressings are commonly used in stage II and III pressure ulcers [26]. In stage I pressure ulcers, it is stated that it is increasingly used [27]. Hydrocolloid dressings offer many advantages in the treatment of pressure ulcers: protection of the skin around the wound, removal of necrotic tissue and loam, and providing a moist wound bed without over-moistening the wound [28]. The hydrocolloid dressings provide a moist wound environment known to be useful for treating the wound. In particular, hydrocolloids accelerate angiogenesis, increase the number of dermal fibroblasts, stimulate the production of granulation tissue and increase the amount of synthesized collagen [29]. The moisture-retaining properties of hydrocolloids soften and rehydrate the necrotic tissue, facilitating autolytic debridement. Hydrocolloids are adhesive and waterproof as well. Some hydrocolloids have been shown to act as viral and bacterial barriers, provided that the dressing remains intact and does not leak [30]. Hydrocolloid dressings may be advantageous for use in areas that are frequently exposed to intensive contamination, such as sacrum. Many studies have examined whether hydrocolloid dressings increase the risk of infection in the wound. It has been reported to reduce the risk of wound infection [31], [32]. Another advantage of hydrocolloid dressings is that they are more economical than gauze for the treatment of pressure ulcers [33], [34] because treatment with hydrocolloid dressings requires less medical examination and fewer dressing changes. If pressure ulcer treatment is not performed properly, the foot, leg, the toe of the wound is amputated and may even cause patient death.

3. Maggot Treatment

Maggot treatment, also known as larval therapy, is based on the principle that larvae of the Lucilia sericata fly are treated with non-healing skin infections such as pressure ulcers, leg ulcers, foot ulcers or chronic wounds that are not actively bleeding [35], [23], [36], [37], [38], [39]. This method was first used by Ambroise Pare in war wounds in the 1500s [40]. The beneficial effects of maggot therapy have been observed in the wounds of soldiers during the Second World War, and research on this subject has become widespread. However, with the widespread use of antibiotics, the use of maggot therapy decreased in the 1940s. Although, with the development of resistance to antibiotics in deep wounds where access to antibiotic drugs is limited, the use of maggot therapy has been brought to the agenda again. Maggot treatment was re-used in the United States, Israel, and the United Kingdom in the 1990s to treat non-healing wounds in Sweden, Germany, Switzerland, Austria, Ukraine, Thailand, and Canada. Nowadays, maggot treatment is used in wound healing in over 30 countries around the world. In the last 20 years, more than 60,000 patients in 2000 health institutions have achieved successful results with this method [35]. This treatment method has been tried and tested with a successful outcome [84] and it continues to be used. In Israel, 87.3% of uses on about 750 injured patients were in the leg or foot and 22.7% in the sacral region [35]. A patient who had his second toe amputated due to venous insufficiency, due to infection and ulcer in the toe, was treated with conventional wound treatment methods for 11 months, but no positive results were obtained. However, maggot treatment was applied and complete debridement of the wound was achieved in 3 days. Thus, suitable conditions for autologous skin transplantation are also provided. The patient's pain was reduced with an appropriate analgesic supplement and no other side effects were observed [41]. Generally, mosquito larvae of the genus Lucilia sericata are used in the treatment. According to animal experiments, the most effective larvae in the treatment of maggot were found to be Calliphoridae and Sarcophagidae families [42]. Among these larvae, facultative Calliphorids (Lucilia sericata) were identified as the most active species. The reasons for preferring mosquito larvae in maggot treatment include; rapid growth cycle, in vitro usability, ease of sterilization of eggs, and larvae are considered to not be interested in internal organs [23], [43], [44].

In maggot therapy, sterile larvae produced in a controlled manner are applied to the wound by being limited to cage-like dressings. Thanks to the larvae used in this treatment method, the wound is kept debrided and disinfected, and new healthy tissue develops faster. Also, more tissue oxygenation is achieved, resulting in reduced necrotic tissue odor [23]. Figure 2 shows the materials used in maggot therapy and the mode of administration.

Figure 2. Lucilia sericata; 2. Maggots; 3. Commercial maggots; 4. Materials used in maggot treatment; 5. Lattice-like dressing; 6. Biobag

There are some disadvantages to the application of maggot therapy. The biggest risk in the application of the method is the sterilization of the larvae used. If non-sterilized larvae are applied to the wound site, sepsis may be caused. Besides, according to case studies, there was also an increase in pain during larval treatment [35]. On the other hand, it should be ensured that the maggots remain in the wound area because the digestive enzymes of the larvae can cause erythema and cellulite. The wound edges should be protected with materials such as hydrocolloids, and the larvae should only remain on the wound [45]. Based on these disadvantages, an attempt was made to produce more durable materials that can be loaded with larvae. Special tools and materials should also be designed to prevent patients with ulcers from crushing larvae in areas where they are treated and where pressure can be applied, such as the underfoot. On the other hand, it is important to note that the larvae should be removed from the wound by squeezing sterile serum after each treatment period. Therefore, it would be more advantageous to design a cover material in which the larvae are directly loaded. Also, the stench of bacteria such as ammonium salts and Pseudomonas secreted by maggots should often be prevented by replacing gauze and pads. Ammonium salts may cause an increase in the patient's body temperature if not absorbed by gauze [44], [46], [42]. In conclusion, maggot therapy is an effective, simple, easy and economical option for the treatment of wounds resistant to conventional treatments [23]. However, it is important to develop additional materials that minimize the above-mentioned disadvantages to make them more accessible and more practical for patients and doctors.

3.1. Maggot Larvae Mechanism of Action

Studies have shown that larvae secrete necrolytic enzymes and disinfect the wound [47]. The larvae secrete enzymes against pathogenic microorganisms. On the other hand, they stop the growth and reproduction of pathogenic bacteria by releasing ammonia, and creating a more alkaline environment in the wound [48], [49], [50], [23]. In several studies, it is emphasized that the substances in the hemolymph and alimentary secretions of the larvae (a mixture of blood and lymph and gastrointestinal secretions) have positive effects on wound healing. These secretions contain urea, ammonium bicarbonate, allantoin and a kind of calcium carbonate-picric acid mixture. Larvae increase epidermal growth factor (EGF) and IL-6 with the help of these secretions. Both factors increase fibroblast secretion and physiologically accelerate wound healing [51], [52]. According to some other studies, calcium and calcium carbonate produced by larvae directly kill bacteria, stimulate phagocytosis and accelerate the development of granulation tissue. The serous exudate formed by the irritating effect of larvae as they move around the wound area also helps to mechanically wash the wound [36], [42], [53]. In general, maggot treatment is thought to have three main effects on the wound: rapid debridement, disinfection, and acceleration of wound healing. In addition, maggots are capable of affecting even the deepest tissues that cannot be accessed surgically [54].

3.2. Sterilization of Maggot Larvae

In order to be successful with maggot therapy, the larvae must be sterilized before they are placed in the wound. Different techniques are used in obtaining sterile larvae. In general, however, a simple method of solution washing is preferred. In this method, adult flies are fed with 20% sugar solution. To stimulate ovulation of flies, flesh-liver parts or fertilizer are used [35], [55], [56], [57]. The eggs on the meat-liver pieces are collected and separated from each other. Eggs are sterilized with 1% sodium sulfite solution added to physiological water containing 2.5% formaldehyde. 400 µg / ml kanamycin monosulphate is added to a mixture of 3% Bakto agar and crushed liver (1: 1 weight/volume) and transferred to the medium [36]. In simple terms; the surfaces of the eggs are disinfected and placed on sterile media. After 2-36 hours, the larvae are hatched from the egg and removed from the medium and washed with distilled water. Sterilize again with physiological saline containing 3.5% formaldehyde and wash once more with distilled water. They are filtered through a fine sieve and stored in sterile ependorf tubes until they are used for treatment [58], [59], [53]. The sterile larvae thus obtained are placed in sterile containers and made ready for use in wound treatment. Sterile larvae stored at 5-80°C and can survive, on average, for five days without losing their viability [45], [35]. These larvae, reaching a length of about 1-3 mm, are left to the necrotic wound for debridement [36].

Today, sterile larvae are commercially produced and marketed by many private companies in the UK, Germany and the United States. The sterile larvae can be supplied from the Faculty of Medicine at Istanbul University and Gulhane Training and Research Hospital in Turkey.

3.3. Development Wound Dressing with Larvae

In conventional larval therapy, cage dressing is generally preferred. For this purpose, the adhesive hydrocolloid materials are cut to contain the wound and the edges are framed with this material so that the wound is exposed. A sterile piece of nylon or dacron is cut so that it is slightly wider than the wound but slightly smaller than the hydrocolloid frame. This gauze is attached to the hydrocolloid frame by adhesive tapes with one end exposed. After the larvae are left in the wound from the exposed end of the gauze, this part is also closed. Sterile tampons are placed on the gauze to ensure resistance. The gauze allows the larvae to breathe as well as facilitates the resistance of the molten necrosis tissue [60], [35], [61].

In recent years, a product called bag Biobag has been developed for maggot treatment. In this product, the larvae are placed between two pieces of gauze of 0.5 mm thick polyvinyl alcohol-hydro-sponge structure, and glued. Since this material is permeable, the larvae can be easily fed and the secretions can penetrate the wound. Besides, since maggots cannot directly navigate the wound, mechanical irritation of the wound edges can be prevented and pain can be reduced. Since the maggot cannot escape from the material, a more hygienic environment is provided [61].

Sterile larvae are sold in tubes containing 300 maggots. Less than 200 larvae are used in small wounds. In larger wounds, up to 1000 larvae can be applied [62], [45]. In general, 10 maggot / cm^2 is recommended for necrosis areas [63].

A new larvae-loading wound dressing designed by our team (MEDISEN R & D) is shown in figure 3. As shown in Figure 3, in the larva-loaded wound dressing, the sterilized larvae are placed in appropriate sized nests and covered with gauze-like structure. Thus, it is planned that the larval spread will be limited only to the wound area. The physical and chemical compatibility of the designed polymeric dressing material is also very important because wound healing is essential to keep the wound area moist and oxygen permeability. Also, the effectiveness of larvae should not be lost and larval secretions should not be prevented from reaching the wound site. On the other hand, the dressing should be easily applied to the wound area and should be easily removed without damaging the wound. Thus, a biocompatible polymeric material is used in the present design.

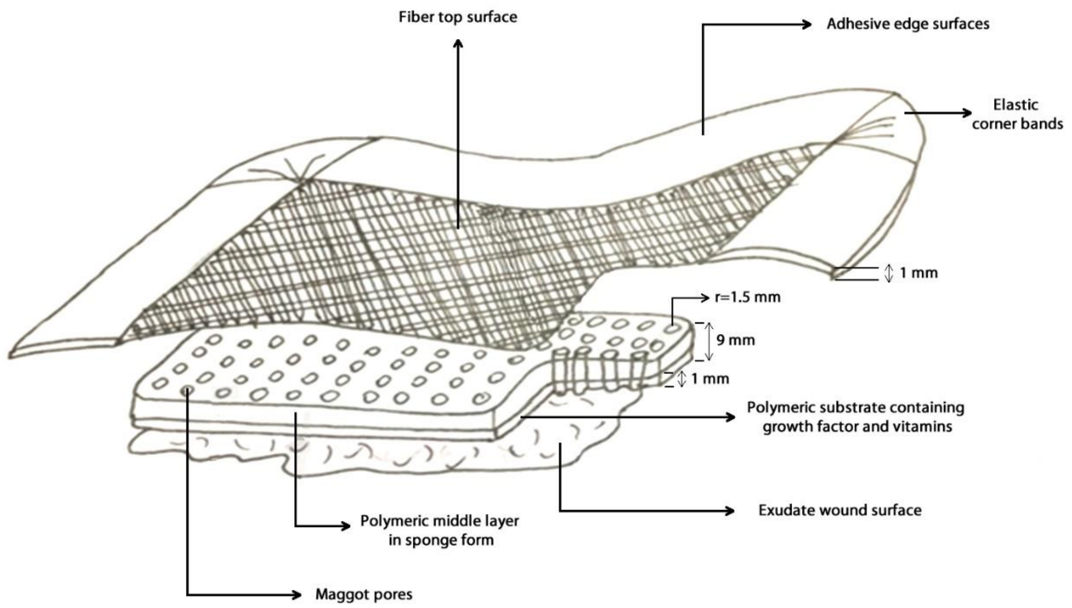

Figure 3. Larvae-loaded wound dressing design

When the patient is moving or entering the shower, the dressing is firmly adherent and waterproof. Wound debridement by larvae loading on the developed dressing is provided by larval secretions, while biocompatible dressing provides oxygen transfer to the larvae and prevents the larvae from dying. Furthermore, the incarceration of the larvae in a restricted area prevents the maggots from escaping and infection of the wound area while the patient is in motion. Thus, it is envisaged to provide treatment outside the clinic. Covering the wound dressing with waterproof material will also allow the patient to enter the shower during long-term treatment processes. In addition, granulation tissue formation in the wound can be accelerated by applying an electric field to the wound dressing and adding a thermal stabilizer.

These recommendations are still in the design and application phase, and if successful results are obtained, patients with many non-healing wounds will be provided with faster healing under higher healing conditions.

4. Conclusion

A pressure ulcer is a type of wound that usually takes a long time to heal, especially in patients with complicated diseases (such as diabetes). where the healing time of pressure ulcers is prolonged and even the wound may become chronic. In addition, pressure ulcer formation is commonly observed in inpatients and wheelchair users due to paralysis and similar causes. There are many adjunctive methods in the treatment of chronic wounds that cannot be cured by local care. These include hyperbaric oxygen therapy (HBO), VAC (vacuum-assisted closure) therapy, larval therapy (maggot therapy), intermittent positive pressure devices, electrical stimulation, growth factors, skin equivalents and stem cell therapy [59]. Some wounds may be resistant to conventional treatment. In this case, maggot/larval therapy is preferred. However, the difficulty in performing such treatments and the problem of sterilization of the larvae limit the frequency of larval choice. Therefore, larvae, should be sterilized by confining them to various materials. With the use of these products, it is aimed to minimize the duration of the patients' stay in the clinic and to fix the larvae to the wound area by preventing the contact of the larvae with the patient, thus eliminating the problem of sterilization and contamination. Thus, it is aimed to keep the patient's quality of life higher during the treatment.

Considering the health expenditures of our country in recent years; a significant portion of the patients treated in hospital stay in hospital due to the treatment of pressure ulcers, and these patients are continuously dressed. This situation imposes a serious cost on our country and individuals. Considering that the majority of consumables used for dressing non-healing wounds are also imported, it should be taken into consideration that treatment costs can grow much more. For this reason, the development of effective dressings and products, especially for the cases of the pressure ulcer type, is of great importance for our country's economy and public health.

References

[1] Yorgancıoğlu Z., İncel N. (1999). Bası Ülserleri Ve Tedavisi, Fiziksel Tıp; 2 (3): 61-66.

[2] Yücel, A. (2008). Bası Yaraları Tanı Ve Tedavisi, İ.Ü Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri Yara Bakımı Ve Tedavisi Sempozyum Dizisi No:67 S.37-5.

[3] Tosun,Z (2007).Bası Yaraları, Selçuk Üniversitesi, Meram Tıp Fakültesi, Plastik Ve Rekonstrüktif Cerrahi A.D.Yara Bakımı Özet Bildiri Kitabı.

[4] Kanj L.F, Wilking S.V, Phillips T.J. (1998). Pressure Ulcers. J Am Acad Dermatol, 38:4 :517-36.

[5] Vanderwee K, Clark M, Dealey C, *et al.* (2007). Pressure Ulcer Prevalence İn Europe: A Pilot Study. J Eval Clin Pract,13: 227-35.

[6] Petersen NC, Bittmann S. (1971). The Epidemiology Of Pressure Sores. Scand J Plast Reconstr Surg, 5: 62-66.

[7] AHRQ 2011 Annual Conference (Agency For Healthcare Research And Quality) https://psnet.ahrq.gov/issue/ahrq-2011-annual-conference (Erişim tarihi : 26.11.19)

[8] Bales I, Padwojski A. (2009). Reaching For The Moon: Achieving Zero Pressure Ulcer Prevalence. J Wound Care 2009; 18(4):137-44.

[9] Bennett G, Dealey C, Posnett J. The Cost Of Pressure Ulcers İn The UK. Age Ageing 2004; 33(3): 230-35,2004.

[10] Hospitals 'named and shamed' on bedsores record which costs NHS £4bn a year, http://www.telegraph.co.uk/health/healthnews/8613764/hospitals-namedand-shamed-onbedsores-recordwhichcosts-nhs-4bn-a-year.html (Erişim tarihi : 23.10.2019).

[11] The National Archives, Pressure-ulcers, https://webarchive.nationalarchives.gov.uk/20101201140958/http://www.institute.nhs.uk/opportunity_locators/calculators/pressure-ulcers.html (Erişim tarihi : 26.11.19).

[12] Alaca,R. (2007). Basınç Azaltıcı Yöntemler, Gata Fiziksel Tıp Ve Rehabilitasyon Ad, Tsk Rehabilitasyon Merkezi,Yara Bakımı Özet Bildiri Kitabı.

[13] Bası Yarası ve İyileşmeyen Yaraların Tedavisi, http://yatakbasiyarasitedavisi.blogcu.com/yatak-yarasi-basi-yarasi-ve-iyilesmeyen-yaralarin-tedavisi-nasi/20319472 (Erişim tarihi : 24.10.19)

[14] Kosiak M, Kubicek WG. (1985). Olson M et al. Evaluation Of Pressure As A Factor İn The Production Of İschial Ulcers. Arch Phys Med Rehabil, 39:623-9.

[15] Feldman DL. (1997). Pressure sores. Georgiade GS, Riefkohl R, Levin LS, eds. Georgiade Plastic, Maxillofacial and Reconstructive Surgery. Baltimore: Williams and Wilkins: 1111-1123, 1997.

[16] Lineaweaver W, McMorris S, Soucy D et al. (1985). Cellular And Bacterial Toxicities Of Topical Antimicrobials. Plast Reconstr Surg; 75: 394-396.

[17] Daniel RK, Terzis JK, Cunningham DM. (1976). Sensory Skin Flaps For Coverage Of Pressure Sores İn Paraplegic Patients: Preliminary report. Plast Reconstr Surg, 58: 317-328.

[18] Parish LC, Witkowski JA. (1989). The infected Decubitus Ulcer. Int J Dermatol, 28:643-7.

[19] Bendy RH, Nuccio PA, Wolfe E, et al. (1964). Relationship Of A Quantitativewound Bacterial Count To Healing Of Decubiti: Effect Of Topical Gentamicin. Antimicrob Agents Chemother, 4:147-55.

[20] Sugarman B. (1987). Pressure Sores And Underlying Bone İnfections. Arch Intern Med, 147:3 :553-5.

[21] Baktıroğlu, S. (2012). Diyabetik Ayak Yarası ve Yara Bakım Ürünleri Yara Bakımında Yardımcı Tedaviler, İstanbul Üniversitesi Tıp Fakültesi ,Genel Cerrahi Anabilim Dalı, Periferik Damar Cerrahisi Ünitesi II. Ulusal Diyabetik Ayak İnfeksiyonları Simpozyumu (UDAİS) İstanbul, 24-26 Mayıs 2012.

[22] Aktaş, Ş. (2012). Kronik Yarada Lokal Faktörler Ve Yardımcı Tedaviler, ANKEM Dergisi, 26 (Ek 2):217-222.

[23] Tuğcu İ, Yavuz F, Safaz İ, Araz E, Alaca R, Tanyüksel M. (2009). Konvansiyonel Tedaviye Dirençli Sakral Bölge Bası Yarasında Maggot Terapi Uygulaması: Olgu Sunumu, Ftr Bil Der - J Pmr Sci,12, 93-96.

[24] Mathes SJ. (1982). The Muscle Flap For Management Of Osteomyelitis. N Engl J Med, 306: 294-295.

[25] Mathes SJ, Alpert BS, Chang N. (1982). Use Of The Muscle Flap İn Chronic Osteomyelitis: Experimental And Clinical Correlation. Plast Reconstr Surg,69: 815-829.

[26] Lohi J, Sipponen A, Jokinen JJ. (2010). Local Dressings For Pressure Ulcers: What İs The Best Tool To Apply İn Primary And Second Care? J Wound Care, 19 (3): 123-27.

[27] European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. Treatment Of Pressure Ulcers: Quick Reference Guide. Washington DC: National Pressure Ulcer Advisory Panel; 2009.

[28] Wicks G. (2007). A Guide To The Treatment Of Pressure Ulcers From Grade 1–Grade 4. Wound Essentials,2: 106-13.

[29] Fletcher J, Moore Z, Anderson I, Matsuzaki K. (2011). Bası Ülserleri Ve Hidrokolloidler, Cilt 2, Baskı 4.

[30] Queen D. (2009). Technology update: Understanding hydrocolloids. Wounds International 1(1). http://www.woundsinternational.com/article.php?issueid=1&contentid=129&articleid=229, (Erişim tarihi: 23.04.2019).

[31] Bowler PG, Delargy H, Prince D, Fondberg L. (1993). The Viral Barrier Properties Of Some Occlusive Dressings And Their Role İn İnfection Control. Wounds; 5(1): 1-8.

[32] Knowles EA, Westwood B, Young MJ, Boulton AJM. (1993). A Retrospective Study Of The Use Of Granuflex And Other Dressings İn The Treatment Of Diabetic Foot Ulcers. Proceedings Of The 3rd European Conference On Advances İn Wound Management; 19-22 October 1993. London: Macmillan; 117-20.

[33] Boulton AJ, Meneses P, Ennis WJ. (1999). Diabetic Foot Ulcers: A Framework For Prevention And Care. Wound Repair Regen; 7(1): 7-16.

[34] Meaume S, Gemmen E. (2002). Cost effectiveness And Wound Management İn France: Pressure Ulcers And Venous Leg Ulcers. J Wound Care; 11(6): 219-24.

[35] Kerstein M, Gemmen E, Van Rijswijk L, et al. (2001). Cost And Cost Effectiveness Of Venous And Pressure Ulcer Protocols Of Care. Dis Manage Health Outcomes 2001; 9(11): 651-63.

[36] Mumcuoğlu K., Özkan A. (2009). Süpüratif Kronik Yaraların Maggot Debridman Tedavisi, Türkiye Parazitoloji Dergisi, 33 (4): 307- 315.

[37] Gönenci R., Yaman M., Altuğ M.E. (2002). Maggot Sağaltımının Cerrahi Alanda Kullanımı, Veteriner Cerrahi Dergisi, 8,116-119.

[38] Sherman R. (2009). Maggot Therapy Takes Us Back To The Future Of Wound Care: New And Improved Maggot Therapy For The 21st Century, Journal Of Diabetes Science And Technology Volume 3, Issue 2.

[39] Michelle LM., Herrington MT., Swenor KM., Lawrence JE. (2011). Maggot Debridement Therapy İn The Treatment Of Complex Diabetic Wounds, Hawaı‘I Medıcal Journal, Vol 70.

[40] Dominic CW Chan, Daniel HF Fong, June YY, Leung NG Patil, Gilberto Kk Leung. (2007). Maggot Debridement Therapy İn Chronic Wound Care, Hong Kong Med J Vol 13 No 5.

[41] Mumcuoglu KY, Ingber A, Gilead L. (1999). Maggot Therapy For The Treatment Of İntractable Wounds. Int J Dermatology; 38:623-7.

[42] Özkan A., Mumcuoğlu KY. (2007). Kronik Venöz Ülserli Bir Olgununmaggot Debridman Tedavisi İle Sağaltımı, Türk Hijyen Ve Deneysel Biyoloji Dergisi, Cilt 64, Sayı 1.

[43] Tanyuksel M, Araz E, Dundar K, Uzun G, Gumus T, Alten B, Saylam F, Taylan-Ozkan A, Mumcuoglu Ky. (2005). Maggot Debridement Therapy İn The Treatment Of Chronic Wounds İn A Military Hospital Setup İn Turkey, Dermatology, 210: 115-118.

[44] Sherman RA, Hall M, Thomas S.(2000). Medicinal Maggots: An Ancient Remedy For Some Contemporary Afflictions. Annu Rev Entomol 2000; 45:55-81.

[45] Courtenay M, Church JCT, Ryan TJ.(2000). Larva Therapy in Wound Management. J R Soc Med, 93:72-4.

[46] Church JCT.(1996). The Traditional Use Of Maggots İn Wound Healing, And The Development Of Larva Therapy (Biosurgery) İn Modern Medicine. J Altern Complement Med, 2:525-7.

[47] Mumcuoglu KY, Ingber A, Gilead L, Stessman J, Friedmann R, Schulman H, Bichucher H, Ioffe-Uspensky I, Miller J, Galun R, Raz I. (1998). Maggot Therapy For The Treatment Of Diabetic Foot Ulcers. Diabetes Care, 21: 2030-2031.

[48] Hinshaw J., Larval Therapy: A Review Of Clinical Human And Veterinary Studies: (2000): http://www.worldwidewounds.com/2000/oct/janet-hinshaw/larval-therapy-human-andveterinary.html (Erişim tarihi: 05.08.2019)

[49] Vistnes LM, Lee R, Ksander GA. (1981). Proteolytic Activity Of Blowfly Larvae Secretions İn Experimental Burns. Surgery, 90:835 41.

[50] Robinson W, Norwood VH. (1934). Destruction Of Pyogenic Bacteria In The Alimentary Tract Of Surgical Maggots Implanted in Infected Wounds. J Lab Clin Med, 19: 581-6,1934.
[51] Simmons SW. (1935). A Bactericidal Principle In Excretions Of Surgical Maggots Which Destroys Important Etiological Agents Of Pyogenic Infections, 30:253-67.
[52] Pavillard ER, Wright Ea. (1957). An Antibiotic From Maggots. Nature, 180:916-7.
[53] Livingston SK. (1936). The Therapeutic Active Principle Of Maggots. J Bone Joint Surg Am; 18:751-6, 1936.
[54] Prete Pe. (1997). Growth Effects Of Phaeniccia Sericata Larval Extracts On Fibroblasts: Mechanism For Wound Healing By Maggot Therapy. Life Science, 60:505-10.
[55] Mumcuoglu KY. (2001). Clinical Applications For Maggots İn Wound Care, Am J Clin Dermatol, 2 (4):219-225.
[56] Wollina U., Liebold K, Schmidt W-D, Hartmann M, Fassler D. (2002). Biosurgery Supports Granulation And Debridement in Chronic Wounds Clinical Data And Remittance Spectroscopy Measurement. Int J Dermatol; 41:635-9.
[57] Simmons SW. (1938). The Culture Of Fly Larvae For Use in Maggot Therapy. Thesis İn Zoology And Entomology. Iowa State College, Ames.
[58] Sherman RA, Wyle Fa. (1996). Low-Cost, Low-Maintenance Rearing of Maggots in Hospitals, Clinics, And Schools. Amer J Trop Med Hyg, 54: 38-41, 1996.
[59] Weil GC, Simon RJ, Sweadner WR. (1933). Larval Or Maggot Therapy in The Treatment Of Acute And Chronic Pyogenic İnfections. Amer J Surgery, 19: 36-48.
[60] Martin J., Hall R., Smith G.V. (1996): Diptera Causing Myiasis İn Man. In Medical Insects And Arachnids, Rp Lane, Crosskey Rw. (Eds.) Capman& Hall, London, 429-464.
[61] Mumcuoglu K.Y., Ingber A., Gilead L., Stessman J., Friedmann R., Schulman H., Bichucher H., Ioffe-Uspensky I., Miller J., Galun R., Raz I. (1999). Pharmacology And Therapeutics Maggot Therapy For The Treat-Ment Of İntractable Wounds. Int J Dermatol, 38, 623-627.
[62] Sherman RA. (1997). A New Dressing Design For Treating Pressure Ulcers With Maggot Therapy. Plast Reconstruct Surg, 100: 451-456.
[63] Fleischmann W, Thoener B. (2000). Biobag - A Live Wounddressing Containing Maggots. Fifth International Conference On Biotherapy, Wurzburg, Germany.
[64] Jarvis A. (2000). Maggots in Orthopaedics: Past, Present And Future. Fifth International Conference On Biotherapy, Wurzburg, Germany.
[65] Thomas S, Jones M, Shutler S, Jones S. (1996). Using Larvae İn Modern Wound Management. J Wound Care, 5: 60-69.
[66] Wu SC, Marston W, et al. (2010). Wound care: The role of advanced wound healing Technologies, J Vasc Surg, 52: (59-66).