Maggot debridement therapy: a systematic review

Abstract

Maggot debridement therapy is used extensively in the UK in both community and hospital situations, but remains a potentially underused modality in many wound care markets. It promotes wound healing by performing three key processes: debridement, disinfection and growth-promoting activity. It can be used for the debridement of non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic of post-surgical wounds. With the increase in chronic diabetic foot wounds, maggot debridement therapy is a promising tool for health professionals dealing with difficult wounds. This article presents an overview of the research evidence surrounding maggot debridement therapy that serves as a guide to health professionals who may be users of this form of treatment now and in the future.

Key words: Maggot Debridement Therapy Chronic Diabetes

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Maggot therapy—also known as larval therapy, biosurgery, biodebridement, maggot debridement therapy (MDT), larval debridement therapy, maggot wound therapy and wound myiasis—all describe a re-emerging therapy in wound care that applies live, medical-grade fly larvae (most commonly of the greenbottle fly, also known as the *Lucilia (Phaenicia) sericata* strain) onto the wound in a controlled environment. The actions of MDT for achieving wound healing are threefold: debridement, disinfection and growth-promoting activity (Sherman, 2009).

Maggot therapy and historical evidence

The beneficial effects of maggots are evidenced in the historical paintings of Mayans, Burmese, Chinese and aboriginal people in Australia (Pritchard and Nigam, 2013). Maggots were used by Napoleon's chief surgeon and by confederate medical officers in the Civil War to enhance tissue granulation and shorten the healing process (Larrey, 1829). However, maggots were not used in the modern era until William Baer used MDT in his treatment of bone and soft tissue infections during World War I (Baer, 1931). Clinical trials were not conducted until 1990, finally achieving Food and Drug Administration approval in the United States in 2004 for its use in (US Food and Drug Administration, 2007):

> 'debriding non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and non-healing traumatic of post surgical wounds.'

Usage in the UK

In practice, MDT remains an advanced modality, appropriate only after conventional therapies fail (Sherman, 2009). Today, with the growing rate of non-healing chronic wounds of the diabetic foot, interest for MDT as a treatment modality has attracted greater attention, and greater consideration as a first-line treatment. It is used extensively in the UK in

both community and hospital situations, but still remains a potentially underused modality in many wound care markets. Although significant clinical evidence is sparse, small clinical trials and case studies reveal a cost-effective, multi-purpose tool in the treatment of a plethora of wound types (*Table 1*).

Table 1. Wound types treated using MDT

Wound type	Supporting literature
Diabetic ulcers	Edwards and Stapley (2010)
Ischemic wounds	Sherman (2009)
Venous stasis ulcers	Sherman and Pechter (1988)
Pressure ulcers	Dumville et al (2009a)
Traumatic wounds	Sherman (1998); Sherman et al (2007)
Post-surgical wounds	US Food and Drug Administration (2007)

Previous meta-analyses

A meta-analysis by Sun et al (2014) investigated the use of MDT in the treatment of chronically infected wounds and ulcers. The study concluded that MDT significantly shortened healing time and significantly improved the healing rate of chronic ulcers. A meta-analysis by Wilasrusmee et al (2013) for maggot therapy in the treatment of chronic ulcers found a 20% greater chance of wound healing using MDT compared with conventional therapies. A meta-analysis by Tian et al (2013) assessing the efficacy of MDT compared with standard of care for diabetic foot ulcers (DFUs) in 356 participants suggested that the MDT group was significantly superior to the control group in several categories, including the percentage of DFUs to achieve full healing, amputation rate, time to healing, and number of antibiotic-free days, but also concluded that larger studies were needed. A systematic review by Zarchi and Jemec (2012) compiled three randomised clinical trials and five non-randomised studies, focusing on the debriding potential of MDT. MDT was found to be significantly more effective as a debriding agent than hydrogel or a mixture of conventional therapy modalities(including hydrocolloid, hydrogel and saline-moistened gauze) (Zarchi and Jemec, 2012).

Debridement

According to the 2013 European Wound Management Association update on the subject, debridement is a basic necessity for inducing the functional process of tissue repair, which makes it a central medical intervention in the management of acute and chronic non-healing wounds (Strohal et al, 2013). With any chronic wound that is stuck in the inflammatory phase, necrotic tissue, fibrin slough and infected debris may not be adequately removed from the wound bed (Sherman, 2014). Traditionally, practitioners have employed various methods to debride wounds, including surgical (sharp), hydrotherapy (high pressure irrigation), sonotherapy (ultrasonic mist), mechanical (wet-to-dry dressings), autolytic (hydrogel) and enzymatic (for example, Accuzyme, collagenase). However, many of these modalities can cause excessive trauma to the wound bed. Surgical debridement with scalpel, scissors and scraper often extends beyond the necessary boundary, as it is difficult to separate and distinguish necrotic tissue or poorly perfused tissue (Waniczek et al, 2013).

Mechanisms of MDT

Debridement remains the strength of maggot therapy. It removes devitalised tissue effectively with minimal tissue trauma (Rafter, 2013). Nonetheless, minor bleeding may be expected (Steenvoorde and van Doorn, 2008). A remarkable reduction in odour emanating from the wound is also characteristic of MDT (Tanyuksel et al, 2005). A full maggot debridement requires an average of 2–3 maggot cycles, lasting 3–5 days (Sherman, 2009). The debridement occurs through two mechanisms. The first is mechanical, wherein the mandibular 'mouth hooks' of the maggots and rough body scratch the necrotic tissue, and the moving body irritates the wound bed (Jarczyk et al, 2008). The second mechanism is more elaborate. During their digestive process, maggots secrete proteolytic digestive enzymes, which liquefy necrotic tissue, enabling the maggots to ingest it (Hobson, 1931; Vistnes et al, 1981). These excretions and secretions have also been found to have deoxyribonuclease (Brown et al, 2012), lipase, glycosidase and chemotrypsin properties, which enable maggots to degrade wound eschar (Andersen et al, 2008; Telford et al, 2010; 2012; Brown et al, 2012). Most recently, maggot excretions and secretions have been found to enhance formation of plasmin and induce fibrinolysis, encouraging the breakdown of the fibrin slough that accumulates in chronic wounds. This keeps the wound free of infection and excessive inflammation to improve wound closure (Van der Plas et al, 2014). A multicentre, randomised controlled trial by Opletalova et al (2012) reviewed 119 nonhealing wounds during a 2-week hospital stay treated either with MDT or conventional dressings. With the percentage of slough as the primary outcome measure, the study concluded that MDT significantly improved the rapidity of wound debridement.

Antimicrobial

The popularity of MDT dramatically fell with the introduction of penicillin by Alexander Fleming in 1928 and the subsequent mass production of antibiotics (Mumcuoglu, 2001). For many decades, antibiotics were successful in eliminating virtually all wound infections. With the rising incidence of drug resistance in recent years, MDT has found a new role in terms of its antimicrobial properties, particularly in its treatment of Gram-positive and Gram-negative bacterial strains, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*,

Methicillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant pathogens (Blueman and Bousfield, 2012; Sun et al, 2014).

In a study by Bohova et al (2014), maggot secretions were found to be effective at reducing the biofilm formation of *Enterobacter cloacae* and *Staphylococcus aureus*, but not *Proteus mirabilis*. Van der Plas et al (2008) associated maggot excretions and secretions with the breakdown biofilms of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and described the ability to ingest and kill bacteria in their digestive tract (Van der Plas et al, 2014). Harris et al (2013) discovered the inhibition of biofilm of *Staphylococcus epidermidis* by the enzyme chymotrypsin in maggot excretions and secretions. Maggot excretions and secretions were found not only to break down established biofilm, but also to prevent biofilm formation on abiotic surfaces such as polyethylene, stainless steel and titanium (Harris et al, 2009; Cazander et al, 2010a) as well as biotic surfaces such as dermal pig-skin implants (Cowan et al, 2013). Maggot excretions and secretions were isolated by Zhang et al (2013) and topically applied to antibiotic-resistant *Staphylococcus aureus* in a mouse-skin infection model, suggesting potential as a topical agent for bacterial infections. It is also noteworthy that maggot excretions and secretions contain ammonia, ammonium bicarbonate and calcium carbonate, which can alkalise wound bases and further inhibit bacterial growth (Prete, 1997).

Effect of maggot therapy on antibiotic use

Rather than inhibiting antibacterial effects, MDT has in fact been found, in high concentrations, to have a synergistic effect on several antibiotics (Cazander et al, 2010b; Van der Plas et al, 2010). Cazander et al (2010b) found this to be true of gentamicin, flucloxacillin, and daptomycin. Arora et al (2011) found an enhanced effect when maggot excretions and secretions were combined with ciprofloxacin. Furthermore, maggot larvae were found to exhibit tolerance to clinical maximum doses of antimicrobials (Peck and Kirkup, 2012). Armstrong et al (2005) investigated the use of MDT in the lower extremity wounds of hospice patients over a span of 6 months. The study found that MDT patients required fewer days of antibiotic treatment, with MDT patients healing an average of 4 weeks earlier than control patients, although the difference was not statistically significant. The authors did comment that, among MDT patients, infections resolved faster and were free of infection for a longer period of time. In a study by Sherman and Shimoda (2004), a cohort of 10 wounds treated with MDT 1–17 days prior to surgical closure had zero postoperative wound infections. However, the same study also found that 32% of the wounds that were not treated with MDT developed postoperative infections.

Anti-inflammatory

The human complement system plays an important role in the activation of the inflammatory response to injury, but inappropriate complement activation can lead to severe tissue damage, as is the case with chronic wounds fixed in the inflammatory phase of wound healing (Cazander et al, 2012). Van der Plas et al (2007; 2009a) reported that the excretions and secretions of maggots inhibit pro-inflammatory responses of human neutrophils and monocytes without affecting the antimicrobial activities of phagocytes. Cazander et al (2013) found inhibition of complement pathways, inhibition of cytokines, and breakdown of complement components. Cazander et al (2012) found that maggot excretions and secretions reduce complement up to 99.9% in all complement pathways through the breakdown of complement proteins.

Growth promotion and other benefits

Laboratory-based clinical studies by Horobin et al (2005; 2006) have shown that maggot excretions and secretions promote fibroblast and keratinocyte migration. Bexfield et al (2010) found that maggot excretions and secretions promote angiogenesis, enhancing vascular endothelial cell migration. Both of these effects can contribute to regranulation effects. Maggot excretions and secretions were found to enhance monocyte and macrophage growth factor production in the form of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both of which stimulate endothelial cell migration and proliferation (Van der Plas et al, 2009b).

Cost reductions

MDT remains a cost benefit and can prevent hospital admission for surgical debridement (Rafter, 2013). It can also reduce the amount of follow-up visits. The most recent meta-analysis showed that the average cost of treatment in patients with diabetic foot ulcers was lower in the MDT group compared with conservative treatment, with medians of £182.54 and £305.46 respectively (Wilasrusmee et al, 2013).

Possible drawbacks

Obtaining maggots

Although 90% of health professionals using maggot therapy during the 1930s were pleased with it (Robinson, 1935), the historical drawback was a difficulty in obtaining viable germ-free maggots, the cost and the effort required to construct a sturdy maggot dressing (Sherman, 2009). Today, 'maggot confinement dressings' have been developed for simple and faster application (Fleischmann and Thoener, 2000). In addition, maggots can now be delivered within 24 hours, and are less expensive than other medical and surgical wound care treatments (Sherman, 2009). A typical chronic wound in the UK costs £2333 to debride—a process averaging 89 days (Bennett et al, 2004). Using MDT, debriding a chronic wound has been estimated to cost £209 a process averaging 5 days (Thomas, 2006).

Pain

As a possible complication of MDT, pain has been a topic of controversy. In a study of 435 patients, 38% reported increased

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A biosurgical maggot wound dressing bag. With advancements in technology improving the application process, maggot debridement process is more viable as an option than ever before

pain during MDT and required treatment with analgesics (Mumcuoglu et al, 2012). In more severe cases, opioids or peripheral nerve blocks may be considered.

In another study by Steenvoorde et al (2005a), a retrospective analysis using a visual analogue scale was used for 41 patients. It was found that diabetic patients experienced the same amount of pain before and during MDT, and 40% of non-diabetic patients experienced more pain during MDT than before. A total of 78% of patients experiencing pain were adequately treated with analgesic therapy.

Limited time window of usage

Another drawback of MDT is found in the maggots themselves. Medicinal maggots are a live species and highly perishable; they must be applied within 24 hours of their delivery. However, in an encouraging post-marketing study, only 1% of maggots arrived late or dead (Nguyen, 2006). Another drawback is the risk of maggots escaping and developing into flies. However, no studies have successfully quantified this occurrence.

Patient anxiety

Patient anxiety and the 'yuck factor' of using maggots as therapy has become considered a point of concern. However, a study surveying a cohort of Dutch patients found this to be a minor concern (Steenvoorde et al, 2005b). A second study interviewing patients undergoing MDT found that the idea of MDT was initially repellant but became acceptable once treatment began (Kitching, 2004).

Clinical studies

One of the first randomised controlled trials conducted by Wayman et al (2000) considered 12 patients with venous leg ulcers that were treated with MDT or hydrogel. After 1 month of therapy, the six wounds in the MDT group had debrided faster (2–3 days) than the control arm (more than 1 month). In the largest and most recent randomised controlled trial by Dumville et al (2009b), 248 venous or mixed venous arterial ulcers were treated either with MDT or hydrogel and followed for 1 month. MDT demonstrated faster debridement, but did not demonstrate faster healing. However, the results of this study may have been affected by differences between the control group and the MDT group. Specifically, extremity compression—a cornerstone of venous ulcer treatment—was utilised among 70% of the control group but only 53% of the MDT group.

In a randomised controlled trial by Markevich et al (2000), 140 patients with non-healing diabetic neuropathic foot wounds received either conventional therapy (hydrogel) or MDT and were studied for 10 days. Compared with conventional therapy, the MDT wounds were successfully

debrided twice as often. Furthermore, MDT wounds achieved complete healing during the observed time period twice as frequently as conventional therapy.

A study by Marineau et al (2011) focused on complex diabetic foot wounds, studying a 23-person cohort that included 11 cases of osteomyelitis. The study achieved a 74% success rate, defining success as, 'full-debridement of the wound bed with enhanced granulation tissue formation with or without full closure of the wound' (Marineau et al, 2011). A retrospective study by orthopaedic surgeons (Wang et al, 2010) followed 25 diabetic foot ulcers and 18 pressure ulcers treated either with MDT or traditional dressings. The MDT group experienced a significantly shorter time to achieve bacterial clearance, granulation and healing of lesions. A prospective case-control study by Paul et al (2009) using MDT of the *Lucilia cuprina* strain of diabetic foot ulcers over the span of 18 months concluded that MDT with *Lucilia cuprina* was as effective as conventional debridement. Tantawi et al (2007) studied 13 diabetic foot ulcers treated with MDT, with complete debridement achieved at a mean of 1.9 weeks and 85% of the ulcers healed within a mean of 7.3 weeks. In one of the largest clinical MDT studies to date, Gilead et al (2012) treated 723 ambulatory and hospitalised patients with MDT—90.5% of which were leg ulcers and 48% of which were diabetic foot ulcers. Complete debridement was achieved in 82.1% of cases, and mean treatment length was 4.65 days. Finally, Sherman et al (2003) followed 20 non-healing diabetic ulcers, including 6 treated with conventional therapy, 6 with MDT and 8 with conventional therapy converted to MDT. It was found that MDT was significantly more effective and efficient in debriding non-healing foot and leg ulcers than conventional care.

KEY POINTS

- Maggot debridement therapy is a treatment that has been around for centuries but has re-emerged over the last few decades, particularly in the UK, as a viable option for wound care
- Maggot debridement therapy is a multi-purpose, cost-effective tool for the treatment of chronic, challenging, difficult-to-heal wounds
- Before it can fully be accepted by the wound care community, more high-quality, randomised controlled trials need to be conducted to prove the strength of maggot debridement therapy

Gangrenous wounds

MDT has also been used to treat gangrenous wounds. A study by Steenvoorde et al (2007) followed 116 infected wounds with signs of gangrenous or necrotic tissue. Following an average of 2.4 maggot applications, 53 healed completely (45.7%), 11 healed almost completely (9.5%) and 12 (10.3%) were free from infection and less than one third of the original wound size.

Conclusion

MDT was an efficient therapy when indigenous tribes first discovered it centuries ago. With the rise of drug-resistant pathogens and the diabetes epidemic, MDT has significantly re-emerged as a useful treatment. MDT is an efficient vehicle of debridement with an innate ability to overcome drug resistance. Although high-quality randomised controlled trials are certainly lacking, the literature documenting the benefits of MDT is promising. With recent advancements in technology improving the application process, MDT is more viable as an option than ever before. Nonetheless, it remains underused as a treatment option. The decision to use MDT is influenced by knowledge of its efficacy in debridement, disinfection and stimulation of healing chronic wounds. Once health professionals and patients are adequately informed, MDT proves to be a quick, easy, safe and cost-effective tool for wound care. **CWC**

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