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A systematic review of maggot debridement therapy for chronically infected wounds and ulcers

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SUMMARY

Objective: This study aimed to systematically evaluate maggot debridement therapy (MDT) in the treatment of chronically infected wounds and ulcers.
Methods: We performed a meta-analysis referring to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). We searched for published articles in the following databases: PubMed, Web of Science, Embase, Wanfang (Chinese), and the China National Knowledge Infrastructure (CNKI). The latest search was updated on March 14, 2014. For dichotomous outcomes, the effects of MDT were expressed as the relative risk (RR) and 95% confidence interval (CI). For continuous outcomes with different measurement scales, we calculated the standardized mean difference (SMD). The pooled effects were estimated using a fixed effect model or random effect model based on the heterogeneity test. Subgroup analyses were performed according to the types of wounds or ulcers.
Results: MDT had a significantly increased positive effect on wound healing compared with conventional therapies, with a pooled RR of 1.80 (95% CI 1.24–2.60). The subgroup analysis revealed that the combined RRs were 1.79 (95% CI 0.95–3.38) for patients with diabetic foot ulcers (DFU) and 1.70 (95% CI 1.28–2.27) for patients with other types of ulcers. The time to healing of the ulcers was significantly shorter among patients treated with MDT, with a pooled SMD of −0.95 (95% CI −1.24, −0.65). For patients with DFU, the SMD was −0.79 (95% CI −1.18, −0.41), and for patients with other types of ulcers, the SMD was −1.16 (95% CI −1.63, −0.69).
Conclusion: MDT not only shortened the healing time but also improved the healing rate of chronic ulcers. Therefore, MDT may be a feasible alternative in the treatment of chronic ulcers.

1. Introduction

Chronic wounds, such as pressure sores and diabetic or vascular ulcers, are associated with high morbidity and, to a lesser extent, mortality.[1] Chronic wounds are notoriously difficult to treat because they usually take the form of non-healing ulcers with fibrotic tissue, dead necrotic slough, and multiple infections.[2] An important issue in wound management is the process called debridement,[3] which is defined as the removal of foreign debris and devitalized or contaminated tissues from a wound bed so that the surrounding healthy tissues are exposed.[4] Clinicians may debride wounds using various methods, including surgery, conservative sharp, high-pressure fluid irrigation, ultrasonic mist, autolysis, or enzymatic agents.[4]

One of the 'old' techniques in wound care is maggot debridement therapy (MDT). MDT is also known as maggot therapy, biodebridement, or larval therapy. In MDT, live and 'medical-grade' fly larvae are applied to the patient's wounds to achieve debridement, disinfection, and, ultimately, wound healing.[5] MDT is indicated for open wounds and ulcers that contain gangrenous or necrotic tissues with or without infection.[6]

MDT uses freshly emerged and sterile larvae of the common green-bottle fly, *Phaenicia* (*Lucilia*) *sericata*, which is a type of artificially induced myiasis raised under controlled clinical

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conditions.[7] This type of larval therapy has several core beneficial effects on wounds and ulcers, including debridement, disinfection, and enhanced healing.[7] The beneficial effects of using larvae were first noted in 1557,[8] but with the introduction and widespread use of antibiotics in the 1940s, it was gradually neglected by doctors.[9] In recent years, with the rising incidence of drug resistance, there has been renewed interest in using maggots in chronic wound management,[9] particularly in treating wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant pathogens.[1]

Current evidence supporting MDT for chronically infected lesions comes from several small clinical trials. To systematically summarize the overall effects of MDT in treating chronic wounds, we performed a meta-analysis by combining the results from different studies with the hope of providing scientific evidence for future clinical applications.

2. Methods

2.1. Data collection

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).[10] We searched for published articles in electronic databases including PubMed, Web of Science, Embase, Wanfang (Chinese), and the China National Knowledge Infrastructure (CNKI) using the following terms and their combinations: ['maggot therapy' OR 'maggot debridement therapy' OR 'larval therapy' OR 'larval debridement therapy' OR 'biodebridement' OR 'biosurgery'] AND ['wound' OR 'ulcer']. The latest search was updated on March 14, 2014. Additional studies were identified from the references listed in the articles retrieved.

2.2. Selection criteria

Studies were included in this meta-analysis if they met the following criteria: (1) provided at least one of the following outcomes: healing rate, time to healing, incidence of infection, amputation rate, antibiotic-free days, or antibiotic usage; (2) compared maggot or larval therapy with other therapies (i.e., conventional therapy); (3) treated chronic wounds or chronically infected lesions; and (4) a relative risk (RR) with a 95% confidence interval (CI) or a mean with a standard deviation was reported or could be calculated from the data presented in the article. The exclusion criteria were (1) duplicated publications, and (2) studies published in any language other than English or Chinese.

2.3. Data extraction

Two graduate students independently read articles and extracted data using a standardized form. Extracted information included the name of the first author, year of publication, country, ulcer or wound type, study design, intervention and control methods, age, number of study subjects, and clinical outcomes. If published data were not available for validity assessments or outcome estimations, we contacted the authors to obtain more information. Discrepancies were resolved by discussion among the research group members.

2.4. Quality assessment

We evaluated the included studies using the quality checklist recommended by the Cochrane handbook for randomized controlled trials (RCTs).[11] The risk of bias among clinical trials was assessed based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. In addition, the Newcastle–Ottawa Scale (NOS) was used to evaluate the non-RCTs.[12] The maximum score was 4 for the selection of study groups, 2 for the comparability of groups, and 3 for the ascertainment of outcomes or exposures. The maximum NOS score was 9, and studies with a score $\geq$6 were considered to be of relatively high quality.

2.5. Statistical analysis

We carried out statistical analyses using Stata 11.0 software (StataCorp LP, College Station, TX, USA). For dichotomous outcomes, the effects were expressed as the RR and 95% CI. For continuous outcomes with different measurement scales, we calculated the standardized mean difference (SMD) and 95% CI.[11] We used Cochran's Q test (significance cut-off point $p = 0.10$) and I^2 ($I^2 < 25\%$, no heterogeneity; $I^2 = 25$–50%, moderate heterogeneity; $I^2 > 50\%$, strong heterogeneity) to test the heterogeneity between the studies.[13,14] The pooled effects were calculated using a fixed effect model or a random effect model based on the heterogeneity test.[15,16] A Galbraith plot was used to detect the potential sources of heterogeneity.[17] A sensitivity analysis was performed by removing one study at a time to assess the stability of the results.[18] Publication bias was assessed using a funnel plot and Egger's test.[11]

3. Results

3.1. Characteristics of studies

Figure 1 illustrates the study selection procedure. In the initial search, 339 potentially relevant articles were identified. After reading the titles and abstracts, we excluded 59 articles that were duplicated publications. We next carefully read the full texts and excluded another 268 studies, including 72 reviews, 84 uncontrolled trials, 22 non-relevant studies, 69 other types of studies such as news, letters, or portraits, and 21 studies published in languages other than English and Chinese. Finally, 12 studies were included in this meta-analysis. The characteristics of these studies are listed in Table 1. The sample size for each study ranged from 12 to 267, with a median sample size of 76. These studies originated

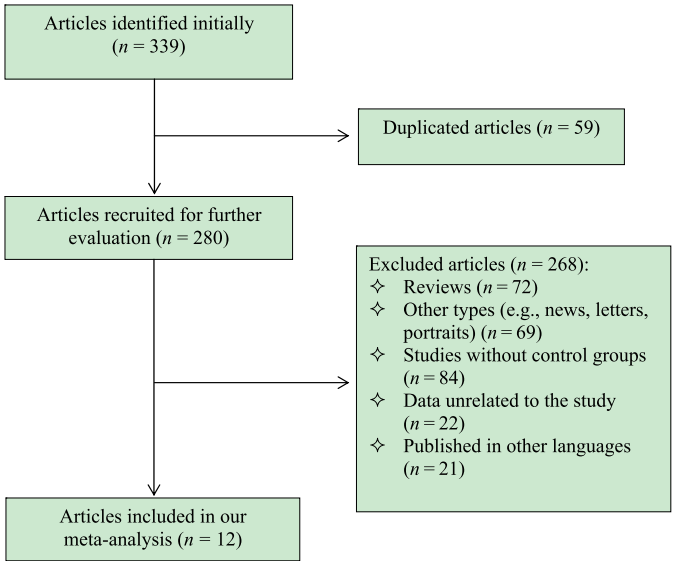

Figure 1. Flow diagram of the study selection procedure.

Table 1
Main characteristics of eligible studies

Author	Year	Country	Type of wound	Study design	Intervention and control	Age, years	Number of subjects	Outcomes
Markevich et al.[24]	2000	Israel	DFU	RCT	MDT	53.6 (SD 15.4)	70	Healing rate
					Hydrogel therapy		70	
Wayman et al.[22]	2000	UK	Venous ulcers	RCT	MDT	58 (range 48–72)	6	Cost of treatment
					Hydrogel therapy	54 (range 40–75)	6	
Sherman[32]	2002	USA	Pressure ulcers	Prospective study	MDT	62 (range 26–85)	43	Healing rate
					Conventional therapy	66 (range 32–91)	49	
Sherman[26]	2003	USA	DFU	Retrospective study	MDT	63 (range 53–74)	14	Healing rate; time to healing; antibiotic usage
					Conventional therapy	68 (range 53–82)	14	
Armstrong et al.[25]	2005	USA	DFU	Retrospective study	MDT	71.7 (SD 6.8)	30	Healing rate; time to healing; incidence of infection; amputation rate; antibiotic-free days
					Standard wound care	72.7 (SD 6.8)	30	
Dumville et al.[3]	2009	UK	Venous leg ulcers	RCT	MDT	73.8 (SD 12.5)	180	Healing rate
					Hydrogel therapy	74.3 (SD 12.8)	87	
Paul et al.[19]	2009	Malaysia	DFU	Prospective study	MDT with *Lucilia cuprina* and subcutaneous insulin	55.3 (range 30.0–69.2)	25	Healing rate; amputation rate; antibiotic usage
					Surgical debridement and subcutaneous insulin	55.3 (range 32.0–82.5)	29	
Soares et al.[23]	2009	UK	Venous ulcers	RCT	MDT	73.8 (SD 12.5)	180	Cost of treatment
					Hydrogel therapy	74.3 (SD 12.8)	87	
Wang et al.[33]	2010	China	DFU/pressure ulcers	Retrospective study	MDT	54.1 (SD 3.7)	23	Time to healing
					Conventional therapy	52.7 (SD 4.1)	20	
Meng and Zhang[20]	2010	China	Crush injury	RCT	MDT	46.0 (SD 6.5)	34	Time to healing
					Conventional therapy	48.0 (SD 3.7)	30	
Wilasrusmee et al.[21]	2013	Thailand	DFU	Retrospective study	MDT	55.5 (SD 12.2)	59	Healing rate
					Conventional therapy	53.4 (SD 11.4)	52	
Mudge et al.,[34]	2014	UK	Venous leg ulcers or mixed etiology leg ulcers	RCT	MDT	N/A	46	Healing rate
					Hydrogel therapy	N/A	42	

DFU, diabetic foot ulcer; RCT, randomized controlled trial; MDT, maggot debridement therapy; SD, standard deviation; N/A, not available.

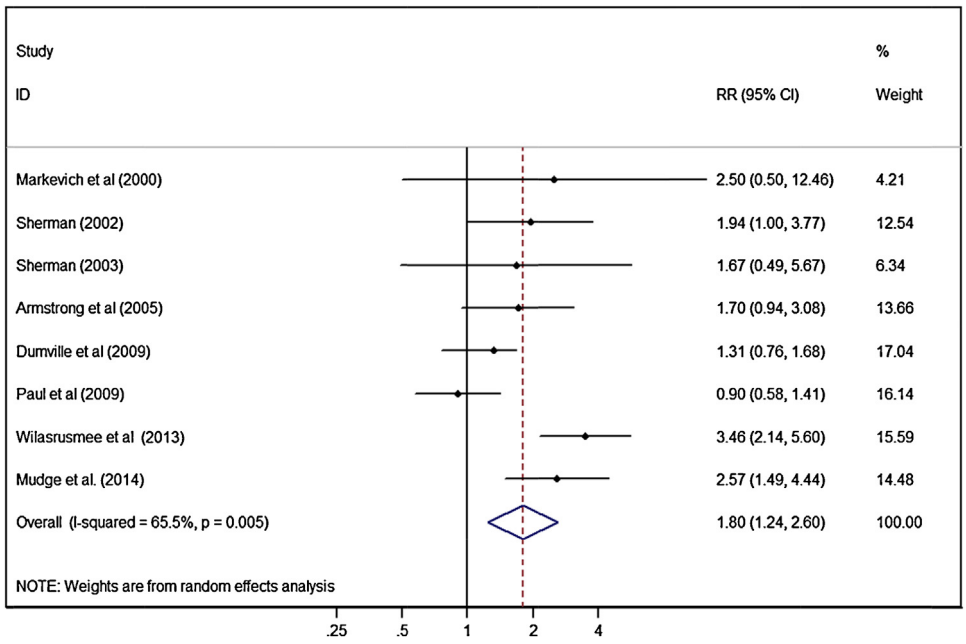

Figure 2. Comparison of the healing rates between the maggot/larval group and the control group.

from six countries or regions (China, UK, USA, Israel, Malaysia, and Thailand). Several studies may have included the same patients, but they estimated different types of outcomes.[3,19] There were 530 subjects who had received maggot or larval therapy and 429 subjects who had received other control therapies (e.g., hydrogel dressing). There was no significant difference in the age distribution between these groups ($p > 0.05$).

3.2. Quality assessment

Of the six RCTs, two[20,21] had two types of source for high risk bias and the other four studies[3,20,22,23] had one type of source for high risk bias. We could not assess the bias of allocation concealment for all six studies. The authors described a random component in the sequence generation process, such as envelope technique[22] or randomly permuted blocks.[3,23] We regarded all studies as being at a high risk of bias for blinding the participants and caregivers because it was not feasible to continue blinding when applying the larval therapy. Except for one study,[24] all of the RCTs described the data of missing patients. For the six non-RCTs, the NOS score of each study ranged from seven to nine, indicating a relatively high quality.

3.3. Pooled effect assessment

3.3.1. Healing rate

Eight studies were eligible for the meta-analysis on the healing rate of MDT. We observed a significant heterogeneity among these studies ($p = 0.005$, $I^2 = 65.5\%$). The pooled RR of wound healing using MDT was 1.80 (95% CI 1.24–2.60) compared with control therapies (Figure 2). We further performed a subgroup analysis by considering the types of wounds. The combined RRs were 1.79 (95% CI 0.95–3.38) for patients with diabetic foot ulcers (DFU) and 1.70 (95% CI 1.28–2.27) for patients with pressure or venous leg ulcers (Table 2).

3.3.2. Infection rate, antibiotic usage, and amputation rate

Only one study[25] applied the infection rate and antibiotic-free days to compare the maggot/larval therapy with the control therapy. In this study, the researchers observed no significant difference in the infection rate between the MDT (80%) and control groups (60%) ($p < 0.05$), but they found a significantly longer antibiotic-free time period in patients receiving MDT (126.8 ± 30.3 days) compared with control groups (81.9 ± 42.1 days) ($p < 0.001$). Two studies were eligible for the pooled estimation of antibiotic

Table 2
Evaluation of eligible studies with risk ratio or standardized mean difference

Factors	No. of studies/subjects	RR/SMD (95% CI)	Heterogeneity test		
			Chi-square	*p*-Value	I^2 (%)
Healing rate					
All studies	8/840	1.80 (1.24–2.60)	20.27	0.005	65.5
Subgroup analysis					
DFU	5/393	1.79 (0.95–3.38)	16.26	0.003	75.4
Other ulcers or wounds	3/447	1.70 (1.28–2.27)	4.01	0.135	50.1
Antibiotic usage	2/82	1.03 (0.87–1.22)	0.65	0.422	0.0
Amputation rate	2/114	0.43 (0.21–0.88)	0.55	0.460	0.0
Time to healing					
All studies	4/195	−0.95 (−1.24, −0.65)	2.36	0.502	0.0
Subgroup analysis					
DFU	3/113	−0.79 (−1.18, −0.41)	0.86	0.650	0.0
Other ulcers or wounds	2/82	−1.16 (−1.63, −0.69)	0.05	0.819	0.0
Cost of treatment	2/279	−0.48 (−1.76, 0.80)	4.12	0.043	75.7

DFU, diabetic foot ulcer; RR, relative risk; SMD, standardized mean difference; CI, confidence interval.

usage. The proportion of antibiotic use was similar in these two groups (27 of 39 (69.2%) in the MDT group vs. 30 of 43 (69.8%) in the control group). The pooled RR (95% CI) was 1.03 (0.87–1.22) (Table 2). The patients in the control group had approximately twice the risk of undergoing amputation compared with the MDT group (RR 0.43, 95% CI 0.21–0.88) (Table 2).

3.3.3. Time to healing

Data from four studies[3,13,14,26] showed that time to healing was significantly shorter in the MDT group than in the control group. The pooled SMD of time to healing was −0.95 (95% CI −1.24, −0.65, $p = 0.502$) (Table 2). In addition, a subset of three studies[3,14,19] (113 subjects) reported the time to healing of DFU, and two studies[13,14] (82 subjects) reported the time to healing of other ulcers or wounds. Both studies provided evidence for the role of MDT in promoting the healing of ulcers (DFU: SMD −0.79, 95% CI −1.18, −0.41; other ulcers: SMD −1.16, 95% CI −1.63, −0.69).

3.3.4. Costs of MDT

Wayman et al.[22] reported the 30-day cost for treating ulcer patients. The costs included nursing, dressing, and larval costs. They showed a total cost for the larva group of £491.87 (including larva costs) compared with a cost of £1039.53 for the hydrogel group. In another study performed by Soares et al., the cost was £172.76 per participant per month for patients treated with MDT compared with £164.70 for patients treated with hydrogel.[23] Considering the significant heterogeneity between these two studies ($p = 0.043$, $I^2 = 75.7\%$), we used a random effect model to estimate the combined difference in the cost (SMD −0.48, 95% CI −1.76, 0.80) (Table 2).

3.4. Sensitivity analysis and bias assessment

We used a Galbraith plot to explore the heterogeneity and to check whether an individual study affected the results of healing rate and time to healing of ulcers. On the Galbraith plot, all of the studies were located within the 95% bounds (the zone of two outer parallel lines drawn at two units over and below the regression) from the standardized mean lnRR and SMD. We conducted leave-one-out sensitivity analyses by removing one study at a time to check whether the individual study influenced the results. We found that the pooled result was not obviously impacted by any single study. A funnel plot and Egger's test showed no statistical evidence of publication bias in the analysis of either healing rate (Egger's test: $p = 0.572$) or healing time (Egger's test: $p = 0.360$).

4. Discussion

Chronic wounds or ulcers are difficult to treat and usually heal slowly when conventional therapies are used. Many of these wounds occur in patients with a poor health status, making ulcer optimization difficult to achieve. MDT, as revealed in this meta-analysis, is more effective and efficient in the debridement of chronic ulcers compared with the conventional treatments.

The utilization of larvae for wound healing has been reported over the last thousand years.[3] A possible explanation of how maggots combat wound infection is that the larvae can ingest wound bacteria and kill them as they pass through their digestive tract.[27] Other mechanisms include irrigation of the wound by increased exudate, the production stimulated by the larvae ingesting necrotic tissues, or dilution of the wound discharge by the maggots' own secretions.[7]

Some previous clinical trials have led to the promotion of MDT as a clinically effective treatment.[28–34] 'Effective' in these trials was defined in various ways, including the promotion of healing, the promotion of debridement, or a reduction in the number of bacteria in the wound.[3] The systematic review of the effects of MDT is essential for guiding its clinical application. In this meta-analysis, we revealed a significant positive effect of MDT on the healing rate of chronic wounds and a shortened time to healing in ulcers. MDT also showed a longer antibiotic-free time period, decreased amputation risk, and similar antibiotic usage compared with conventional therapies. With the increased public acceptance and medical awareness, MDT may be used more widely for superficial infections in the future. For patients with drug resistance, chronic infections, immunosuppressive illnesses, or diabetes, MDT may even become the first-line treatment. Currently, doctors usually consider MDT to be a last resort to treat infected ulcers with peripheral vascular diseases when conventional treatments have failed. It is recommended that early aggressive surgical debridement with intravenous antibiotics in combination with MDT may be more effective than these treatments alone.[3]

MDT can reduce overall antibiotic use, prevent hospital admissions, and decrease the number of outpatient visits. It is a relatively cheap method and may save medical costs, as mentioned above, and reduce hospital bed occupancy. In this meta-analysis, only two articles were eligible for the cost-effective analysis. More studies are needed to compare the cost and effectiveness of MDT compared with traditional therapies, such as hydrogel dressing. The complications of MDT are reported to be few and minor.[1] Some authors noted a mild febrile reaction after applying larvae to the wound. Ethical problems, including patient recruitment and staff acceptance, are limited. MDT is usually well tolerated by the patient, although the escape of larvae is sometimes observed; this can be overcome by creating appropriate dressings.[1]

It is important to select appropriate indexes together with well-designed trials to judge the effectiveness of MDT. In addition to the common outcomes mentioned above, some studies have explored the time to debridement by MDT. For example, a study with 105 patients found that debridement by MDT was significantly faster than the control therapy during the first week of treatment but reached the same level by day 15.[31] Dumville et al. also reported that there was no difference in the time to debridement between the two groups, but that the rate of debridement at any time in the MDT group was about twice that of the hydrogel group.[3] However, there are limited data for meta-analyses. Gray performed a meta-analysis in 2008 that involved four studies to identify the efficacy of MDT for the removal of necrotic tissue and its impact on wound healing.[4] Four studies all reported that MDT led to more rapid debridement than conventional therapies did. However, the author stated that there was insufficient evidence to conclude that MDT is as effective as, or more effective than, other debridement methods, due to the methodological limitations of these studies.[4] For example, there was only one prospective randomized clinical trial, but it used cost outcomes rather than efficacy as its main outcome measure. Since then, several new studies on the effects of MDT on chronic wounds or ulcers have been reported, making MDT eligible for an updated meta-analysis. By searching relevant databases, we included 12 studies for this systematic review, including 530 subjects who had received maggot or larval therapy and 429 subjects who had received control therapies. By using multiple outcome measures, we found that the healing rate was significantly higher and the time to healing was shorter in the MDT groups compared to control groups.

Although we identified positive effects of MDT on treating wounds or ulcers in our current updated meta-analysis, several limitations in this study should be noted. First, the number of relevant studies eligible for the meta-analysis was relatively small, resulting in lower statistical power. Second, the therapies used in

the control groups varied in different studies, which may have influenced the effect estimation of MDT. Third, in some non-RCTs, MDT might have been used primarily as a salvage tool when almost all else had failed, which would lead to biased healing outcomes. Finally, most of the studies were carried out in Asian populations, thus limiting the generalization of the findings. Moreover, the different patient selection criteria, chemotherapeutic protocols, and follow-up periods were also possible explanations for the heterogeneity in the studies.

In conclusion, MDT not only shortened the healing time but also improved the healing rate of chronic ulcers; therefore, it may be a feasible alternative in the treatment of chronic ulcers.

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Conflict of interest: The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.03.1397.

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