Safety, effectiveness and economic aspects of maggot debridement therapy for wound healing

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Abstract
Background: Maggot therapy has recently attracted considerable attention as an emerging debridement technique for wound healing. This study aimed to review the safety, effectiveness and economic evaluations of Maggot Debridement Therapy for wound healing.

Methods: To retrieve the relevant evidences, the Cochrane Library (until September 2014) was searched by appropriate keywords, using free text and Mesh. Systematic reviews, HTA reports and economic evaluation studies that compared larval therapy with other debridement therapies, such as hydrogel in patients with various kinds of ulcers in terms of side effects, the wound healing rate, the healing time, and cost per QALY, were included.

Results: Five studies met the inclusion criteria which showed that healing with larval therapy happened a little earlier than the usual methods and that pain perception in larval therapy was a little more than usual methods (as by anesthetic conventional methods). However, the quality of life of those patients who received larval therapy was better and they showed a greater tendency to larval therapy as it was relatively safe and had a low rate of side effects.

Conclusion: It seems that larval therapy has several advantages such as rapid wound debridement, infection elimination, pain control and ulcer healing. The use of larval therapy has the potential to reduce side effects and decrease the need for amputation.

Keywords: Larval Therapy, Wound Debridement, Ulcer Healing, Median Nerve, Electromyography, Ulnar Nerve, Ulnar-to-Median Nerve Anastomosis, Nerve Injury.


Introduction
Debridement is a stabilized method in wound management. This method usually results in the reduction of infection and improvement of ulcer that is made through removing the dead and polluted tissues. A few methods are used for the debridement of chronic wounds including mechanical, surgical, autolytic and enzymatic methods. Each of these methods has some disadvantages such as limited effectiveness, need to anesthesia, and pain and mechanical damage to the lower healthy tissue (1). Untreatable diabetic foot ulcers include 25-50% of all diabetic hospital admission. More than 60,000 to 70,000 annual amputations in the USA are due to this subject. Almost 15% of all diabetic patients have...
one or more foot ulcers, and 15-25% need amputation at the end (2). In the meantime, one of the debridement methods that has been recently taken into consideration is the debridement technique through larval therapy (1). Debridement through larval therapy is currently used extensively in Britain and USA where larval sterile exists commercially. This method is used as one of the therapeutic methods for the treatment of infectious diabetic foot ulcers. Lucilia Caprina fly is used for this purpose (3). For 70 years, Maggot Therapy has been known as an effective way for debridement and treatment of ulcers. Medical larva secretes the solvent enzymes from themselves that can solve the necrotic tissue, disinfects the wound and accelerates the wound healing (4). Larva destroys the dead tissues and activates the live and healthy tissues, cleans the wound from bacteria, while does not damage the live and healthy tissues. These worms eat the necrotized and infectious tissues and then leave the wound. In larval therapy, the larva of sterilized insect after coming out of the egg is put on the wound to feed from the dead tissues. When larvae are matured, they will not feed from the wound anymore, so, they are replaced. Larval therapy is a good treatment option for the wounds with dead tissues, purulence and gangrenous ulcers. In general, application of larva for a wound as the last defensive method is commonly used when the patient had received antibiotic and surgical treatment for months and no success was obtained.

In addition, larval therapy is useful when patient’s health is at risk or when he/she is not able to tolerate the antibiotic. Most patients have no specific feelings during larval therapy, but some of them may have the feeling of itching and tickling (5).

In addition, controlled clinical studies indicated that larval therapy may be safe and effective in many of other diabetic and nondiabetic ulcers such as pressure ulcer, leg thrombosis ulcers, preparation of wound bed before surgical closure and other types of traumatic, infectious and vascular ulcers. Due to the use of this technology in different countries, Food & Drug Organization of the United States has confirmed the prescription and use of Maggot therapy and enacted regulations for it. Also, in other countries, Maggot therapy has been used as a kind of drug and at least 24 laboratories in more than 30 countries in the world in 2009 have worked to prepare therapeutic maggots to be used in therapists (6). This study aimed to review the studies on this subject and conclude the results and help the policy makers to use this method to treat all kinds of ulcers in Iran.

Research Questions
This assessment article addressed the following question: “What are the safety, effectiveness and economic aspects of Maggot therapy compared to the hydrogel, wet saline gauze and other conventional treatments used to treat the wounds and ulcers in the population of patients suffering from wounds and ulcers in the light of pre-defined outcomes?”

Study Objectives
This study aimed to systematically assess the safety, effectiveness and economic aspects of Maggot therapy compared to the other conventional treatments for the treatment of wounds and ulcers in the population of patients suffering from wounds and ulcers in the light of pre-defined outcomes.

Methods
Literature Search
The present study was a systematic review to study larval therapy for the treatment of wounds and ulcers. In this study, the electronic Cochrane Library (this database was selected because in this study, the researchers seek to find high quality studies with levels 1 and 2 of clinical evidences) was searched up to September, 2014 systematically (Appendix 1). No language or time limitation was taken into account for searching the papers. At this stage, 69 articles were found, but after the review 62 unrelated articles were removed. After con-
sidering the inclusion and exclusion criterion, five articles were ultimately included in the final assessment phase, and two studies were removed. This assessment was done independently by two researchers and in case of any disagreement between them, a third person entered into the process (Tables 1 and 2) (Fig. 1).

**Inclusion and Exclusion Criteria**

**Study Design**

Systematic reviews, health technology assessment and economic evaluation studies were searched, as they provide the most confident forms of evidence.

**Intervention**

Larval therapy

**Population**

Population of patients suffering from wounds and ulcers

**Comparators**

Hydrogel, wet saline gauze and other conventional treatments

**Outcomes**

The outcomes of the review were as follows:

- Side effects of the treatment
- Wound healing time
- Wound healing rate
- Cost per QALY

**Quality Appraisal Method**

Most of the included studies had a desirable quality (using CASP checklist); nonetheless, quality of the study was not used as a tool for exclusion of the articles.

**Synthesizing Method**

Based on the thematic synthesis, the obtained results from the studies were qualitatively analyzed in three subgroups of safety, effectiveness and economic evaluation.

**Results**

**Literature Search**

Out of the five retrieved articles, one
study was on health technology assessment (7), two articles were related to economic evaluation (8,9), one study was a multicenter randomized controlled trial (3) and one study was a systematic review (1). Out of the included articles, two studies were conducted in 2012 (3,4), two studies in 2009 (7,8) and one study in 2000 (9) (Table 3).

A) Safety

Three hundred forty side effects were seen in 131 patients. Of them, 13.8% were categorized as serious, and 14.6% were events with loose larvae, 13.5% with bagged larvae, and 13.5% with hydrogel. More patients in the combined larval therapy group were affected by one or more adverse events than patients in the hydrogel therapy group (51.7% v 43.7%), but this difference was not statistically significant ($\chi^2 = 2.65, df = 1, p = 0.10$) (7).

B) Effectiveness

B-1- Wound Healing Rate: Out of 105 patients included in the study, 51 persons had received Maggot therapy and 54 received the standard therapy. Slough rate had no significant difference on the 1st, 15th and 30th days between the two groups. Slough rate on the 8th day showed a significant difference. Healing rate on the 15th day in the two groups was significantly different, but no significant difference was observed on the 8th and 30th days. Moisture balance from the 1st to the 15th day was similar in the two groups. Mild pain significantly existed in both groups with a significant difference. Infectious ulcers number from the 1st to the 15th days was reduced in Maggot therapy, but no significant difference existed in bacterial culture in MRSA (Methicillin-Resistant Staphylococcus Aureus) or P aeruginosa: A type of pathogenic bacteria). Three patients in the control group showed side effects. The number of patients that felt the rise in the wound on the 8th day was equal. Wound care was significantly longer in the conventional treatment group than the Maggot therapy group regardless of the fact that local anesthesia time for debridement was quicker with Maggot therapy. Debridement with Maggot therapy did not increase the healing rate. Pain in both groups was similar and low, but anesthetic substance was used in the control group. Bacterial cultures were not different between the two groups. The patients did not remain silent for the Maggot effects/all patients requested it (3).

B-2- Wound Healing Time: The summary of Sherman systematic review study indicated that the debridement via Maggot therapy is significantly more effective than hydrogel or a combination of other conventional therapy methods such as hydrocolloid, hydrogel and wet saline gauze on the reduction of wound healing time.

Table 1. The List of the Included Studies

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Title</th>
<th>Year</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zarchi &amp; Jemec (4)</td>
<td>The efficacy of maggot debridement therapy – a review of comparative clinical trials</td>
<td>2012</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>2</td>
<td>Dumville et al. (7)</td>
<td>Larval therapy for leg ulcers (VenUS II): randomized controlled trial</td>
<td>2009</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>3</td>
<td>Opletalova et al. (3)</td>
<td>Maggot Therapy for Wound Debridement: A Randomized Multicenter Trial</td>
<td>2012</td>
<td>Multicenter Randomized Controlled Trial</td>
</tr>
<tr>
<td>4</td>
<td>Soares et al. (8)</td>
<td>Cost effectiveness analysis of larval therapy for leg ulcers</td>
<td>2009</td>
<td>Economic Evaluation</td>
</tr>
<tr>
<td>5</td>
<td>Wayman et al. (9)</td>
<td>The cost effectiveness of larval therapy in venous ulcers</td>
<td>2000</td>
<td>Economic Evaluation</td>
</tr>
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</table>

Table 2. The List of Excluded Studies with Exclusion Reason

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Year</th>
<th>Exclusion Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maggot debridement therapy with Lucilia cuprina: a comparison with conventional debridement in diabetic foot ulcers (2)</td>
<td>2009</td>
<td>Case Control Study</td>
</tr>
<tr>
<td>2</td>
<td>Maggot versus conservative debridement therapy for the treatment of pressure ulcers (10)</td>
<td>2002</td>
<td>Cohort Study</td>
</tr>
</tbody>
</table>
Table 3. The Features of the Included Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country /year</th>
<th>Study Type</th>
<th>Studied Population</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarchi &amp; Jemec (4)</td>
<td>Denmark /2012</td>
<td>Systematic review</td>
<td>3 randomized controlled trials and 5 controlled clinical trials including population of patients infected with all types of wounds</td>
<td>Larval therapy in comparison to hydrocolloid, hydrogel and wet saline gauze</td>
<td>Rate of improvement with debridement</td>
<td>These studies introduced larval therapy as a therapy more effective than hydrogel, or a combination of conventional therapeutic methods such as hydrocolloid, hydrogel and wet saline gauze, significantly. Larval therapy reduces the debridement time significantly. Mean score of pain related to ulcer in larval therapy comparing to hydrogel was higher. In other consequences, no significant difference existed.</td>
</tr>
<tr>
<td>Dumville et al (7)</td>
<td>UK /2009</td>
<td>Health technology assessment</td>
<td>Out of 105 patients included in the study, 51 persons had received maggot therapy and 54 persons common therapy.</td>
<td>Larval therapy in comparison to standard debridement technology</td>
<td>Time required for improvement of the biggest qualified wound. Time for debridement, quality of life related to health, bacterial burden, resistance to meticillin staphylococcus aureus, side effects, and ulcers related to pain</td>
<td>Healing rate on 15th day in two groups was significantly different, but on 8th and 30th days, difference was not significant. Therapy care in common cares group was significantly more than maggot therapy. Even regardless of local anesthesia time, debridement with maggot is quicker.</td>
</tr>
<tr>
<td>Opletalova et al (3)</td>
<td>France /2012</td>
<td>Multicenter Randomized controlled trial</td>
<td>Larval therapy in comparison to standard therapy</td>
<td>Improvement rate of wound surface on 15th day.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soares et al (8)</td>
<td>UK /2009</td>
<td>Economic evaluation</td>
<td>267 patients infected with venous ulcers or a combination of venous and arteriole leg ulcers with the coverage of at least 25% of necrotized slough tissue</td>
<td>Larval therapy in comparison to hydrogel</td>
<td>Increasing costs for any day without ulcer (analysis of cost, effectiveness) and increasing costs for every year together with (analysis of cost-appropriateness)</td>
<td>Larval therapy group costs was averagely 96.70 Pounds annually for every participant was more than hydrogel and they were improved averagely 2.42 days earlier and had higher quality of life related to health. This difference between two QALY groups was 0.011. None of these differences was significant. Incremental cost effectiveness ratio in basis level was 8826 Pounds for each QALY and 40 Pounds for days without ulcer.</td>
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<tr>
<td>Wayman et al (9)</td>
<td>UK /2000</td>
<td>Economic evaluation</td>
<td>12 patients infected with venous ulcers were placed in two larval therapy group or control group with standard therapy.</td>
<td>Larval therapy in comparison to standard therapy (hydrogel)</td>
<td>Effective debridement and mean therapeutic cost</td>
<td>Larval therapy cost was 78 pounds in comparison to 136 pounds in control group. Study demonstrated clinical effectiveness and cost effectiveness of larval therapy in debridement of venous wounds.</td>
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</table>

Notwithstanding, quality of the included studies in this review was lower than the appropriate value and there were important differences in the use of other therapies such as compressing that may affect the both debridement and healing between the two groups and inappropriately on the short follow-up times. Therefore, the quality of these studies challenges this fact that maggot therapy shortens the wound healing time. The low quality of data used to assess Maggot therapy effectiveness requires conducting further higher quality researches (1).

In the health technology assessment study of Dumville, from July 2004 to May 2007,
1,712 persons that had foot ulcer were screened. In that study, 267 persons were selected among 18 therapy institutes. The wound healing time was not different between groups and the healing rate of the two types of larva showed no difference and both groups were combined. The mean healing time was 236 days for the larval group and it was 245 days for the hydrogel group; the adapted risk for larvae was 1.13 compared to hydrogel group; and debridement time of loose larva was lower compared to bagged larva and hydrogel. Debridement time between the three groups was significantly different; the mean debridement time for free larva was 14 days and 28 days for packed larva and 72 days for hydrogel. When the two larva groups were compared, supposing fixed conditions, the difference was not significant. Debridement in each one of larvae groups was almost two times more than that of hydrogel group. The risk ratio for the combined larvae group compared to hydrogel group was 2.31. The summary of basic physical scores for combined larvae group was 33.3 and it was 35.9 for hydrogel group. The summary of basic mental scores for combined larvae group was 46.9 and it was 47.2 for hydrogel group. The summary of physical scores was not significant between the groups. Bacterial burden was not significant between groups. The scores of pain related to ulcer in larvae group was almost two times more than that of hydrogel group, and the difference was significant between the larvae and hydrogel groups. No evidence implying the reduction of larvae healing time was seen compared to hydrogel group, and no evidence implying a difference between quality of life and bacterial quality was found. Larva was a more effective debridement agent than hydrogel. The outbreak of MRSA showed no significant difference between larva group and hydrogel group. Low MRSA among patients from population was different from previous studies. MRSA may be reduced without the use of Larva (7).

C) Economic Evaluation
C-1- Cost-Effectiveness: Cost effectiveness study of Soares indicated that larval therapy costs are more than hydrogel annually, 96.70 Pounds for each participant on average. The participants who received larval therapy were improved 2.42 days earlier than those received hydrogel on average; and those who received larval therapy had a slightly better health related quality of life. The annual difference of QALY was 0.011, but none of these differences was significant. Incremental cost effectiveness ratio at the basic level was obtained to be 8,826 Pounds for each QALY and 40 Pounds for days free of ulcer. Debridement of leg ulcers via larval therapy will probably have the similar health advantages and similar therapeutic costs compared to hydrogel (8).

A study on cost effectiveness by Wayman indicated that larval therapy cost was 78 Pounds compared to 136 Pounds for the control group. This study proved the clinical effectiveness and cost effectiveness of larval therapy in debridement of venous ulcers (9).

Discussion
One of the main aspects of wound management may be the removal of the dead tissues from the wound surface. In addition to healing the wound, debridement stimulates the healthy cells to grow. No difference was observed between free and packed larva’s effect in debridement with different methods. Also, no significant difference was found between larval therapy and other standard methods. MRSA in both larval therapy and common methods is controllable, but larval therapy seems to reduce the wounds healing time significantly more than other common methods. The mean days required for debridement of the wound for larval therapy was significantly lower than the common methods. In addition, the time of therapeutic employees and consumables for anesthesia during the therapy, based on the common methods, has no cost in larval therapy. In addition to the activities related to anesthesia, more attention...
needs to be paid to the treatment of patients with common methods. The mean score for the felt pain in larval therapy within the first 24 hours and before the first removal by larvae, was significantly more than other methods, and it is used in common methods such as anesthesia. This high pain mean is related to larval therapy processes and methods and is transient, and may not affect the quality of patients’ health when continuing the therapy. Larval therapy is relatively safer and has lower side effects. The most important effectiveness of using larval therapy is its relative acceleration of the wound healing time. The cost of using this method is low and is more cost-effective compared to other wound healing methods.

Conclusion
According to the included studied, it is concluded that larval therapy as a type of therapy has various advantages such as quick wound debridement and destruction of infection, pain control and wound healing. The use of larval therapy results in lower side effects and reduces need to amputation.

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References

Appendix 1
The Search strategy in Cochrane was as follows:

| #1) | Maggot Therapy | 25 |
| #2) | Larval Therapy | 57 |
| #3) | #1 or #2 | 69 |