Evidence Table


Study Type: Randomized controlled trial.
Study Aim: To compare the effectiveness of larval therapy and a standard debridement technique (hydrogel) for healing sloughy or necrotic leg ulcers.

Outcomes
- **Primary:** Time to complete healing of ulcer.
- **Secondary:** Time to debridement, health-related quality of life, microbiology (bacterial load and MRSA), ulcer-related pain, adverse events.

Design
- **Number of subjects:** N=267 (n=94 loose larvae, n=86 bagged larvae, n=87 hydrogel)
- **Description of study population:** Loose larvae group: 38.3% male; mean age=74.1 ± 12.9; 76% with mean area of ulcer >5 cm, 65% with duration of ulcer >6 months; Bagged larvae group: 33.7% male; mean age=73.5 ± 12.2; 77% with mean area of ulcer >5 cm, 47% with duration of ulcer >6 months; Hydrogel group: 50.6% male; mean age=74.3 ± 12.8; 75% with mean area of ulcer >5 cm, 60% with duration of ulcer >6 months.
- **Inclusion criteria:** Venous or mixed venous and arterial leg ulcers (Ankle brachial pressure index ≥0.6); ≥25% of wound covered by slough or necrotic tissue; non-healing ulcers with an area of ≤5cm².
- **Exclusion criteria:** Pregnant or lactating; allergic to hydrogel; grossly edematous legs; taking anticoagulants.
- **Intervention:** Patients were randomized to receive loose larvae (Zoobiotic; Wales), bagged larvae (Biomonde; Germany) or hydrogel (Purilon; Denmark) during the debridement phase. Sterile Lucilia sericata larvae were used for the two interventions. The number of larvae was according to manufacturers’ guides. Compression bandaging could not be used during larvae therapy. Larvae were left on the ulcers for 3-4 days. If further larval therapy was required, patients used standard bandaging and hydrogel while more larvae were ordered. The control group received hydrogel covered with a knitted viscose dressing as well as compression when appropriate. In the phase after debridement, all participants received a standard knitted viscose bandage with or without compression.
- **Source of outcome data:** Clinical evaluation; healing was assessed by two independent masked evaluators.
- **Length of follow-up:** Maximum of 12 months.

Validity
- **Blinding?** Outcome assessment was blinded.
- **Appropriate randomization procedures?** Yes, remote telephone randomization service.
- **Appropriate comparison intervention?** Yes.
- **Treatment/control groups comparable at baseline?** Yes.
- **Other than intervention, was care/follow-up similar in each group?** Compression bandaging was different—it was not possible in the groups receiving larvae therapy.
• Adequate compliance with intervention? Yes.
• Sufficient statistical power? Yes.
• Intention to treat analysis? Yes, for primary analysis.
• Completeness of follow-up: 248/267 (93%) received the allocated treatment.
• Industry funding? No, funded by UK National Institute for Health.
• Conclusions regarding validity of methods: Valid methods. Outcome assessment was blinded. It was not possible to blind patients or clinicians.

Results

Primary outcome: Median time to healing

<table>
<thead>
<tr>
<th></th>
<th>No. days (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larvae groups*</td>
<td>236 (147-292)</td>
<td>1.13 (0.76-1.68)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>245 (166-not estimable)</td>
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</tbody>
</table>

* Two larvae groups combined since results were similar for this outcome

Time to debridement

<table>
<thead>
<tr>
<th></th>
<th>No. days (95% CI)</th>
<th>p-value (3 groups)</th>
<th>p-value (2 larvae gps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagged larvae</td>
<td>28 (13-55)</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Loose larvae</td>
<td>14 (10-17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogel</td>
<td>72 (56-131)</td>
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Bacterial load

There was no significant difference in the bacterial load over time between the combined larvae group and the hydrogel group, p=0.75

MRSA eradication

18/267 (6.7%) had positive swab for MRSA at baseline
Of these, MRSA was eradicated during the debridement phase in:
Bagged larvae  5/5 (100%)
Loose larvae  4/7 (57%)
Hydrogel  3/6 (50%)

Note: Percentages can be misleading with small sample sizes and number of events.
Adverse events

Overall, rate of adverse events did not differ among groups

Ulceral-related pain score (for the 24 hours before removal of the first debridement treatment): Significantly higher for participants in both larvae groups than the hydrogel group (p<0.001)

Pain scores beyond the first debridement treatment (3-4 days) were not reported.

Authors’ Conclusions

“Larval therapy did not improve the rate of healing of sloughy or necrotic leg ulcers or reduce bacterial load compared with hydrogel but did significantly reduce the time to debridement and increase ulcer pain”.

Reviewer’s Conclusions

In this well-designed randomized controlled trial, larvae therapy did not increase time to healing, but did significantly decrease time to debridement. Ulcer-related pain after approximately 3 days was higher in the larvae groups; longer term pain was not assessed. The proportion of ulcers with MRSA was too small to draw conclusions about the impact of larvae treatment on MRSA eradication.