Larval therapy for leg ulcers

Introduction

Venous leg ulcers develop from underlying venous disease and are one of the most common chronic wound types. High compression bandaging is effective but only about 50% of leg ulcers are healed within 16 weeks, leaving scope for further improvements.

An important aspect of wound management is thought to be removal of devitalised tissue from the surface of the ulcer; a process called debridement. It has been suggested that larval therapy debrides wounds more swiftly than standard treatments as well as stimulating healing, reducing bacterial load, and eradicating meticillin resistant *Staphylococcus aureus*. Larvae used for medicinal purposes are available in loose and bagged formulations. Although larval therapy is increasingly used it has been evaluated in just one published randomised controlled trial, which included only 12 patients with venous leg ulcers and reported debridement rather than healing as the surrogate outcome. Evidence for any antimicrobial activity with use of larvae comes mainly from laboratory studies.

We undertook a randomised controlled trial to evaluate the clinical and cost effectiveness of larval therapy compared with a standard debridement treatment (hydrogel) on time to complete healing of leg ulcers, time to debridement, cost of treatments, health related quality of life (including ulcer pain), and microbiology.

Methods

This was a pragmatic multicentre, randomised, open trial with equal randomisation, carried out in 22 centres in the United Kingdom from July 2004 to May 2007.

Participants were recruited from leg ulcer clinics, community nurse caseloads, hospital wards, and hospital outpatient departments (for example, dermatology or surgery). Participants gave written informed consent. Eligible participants had venous or mixed venous and arterial leg ulcers (assessed as an ankle brachial pressure index $\geq$0.6) with at least 25% of the wound covered by slough or necrotic tissue (larval therapy would not normally be used on wounds with less coverage). We considered ulcers with an area of 5 cm^2 or less as eligible if they were non-healing (defined as no change in area over the preceding month). If a patient had multiple ulcers we chose the largest eligible ulcer as the reference lesion. Patients were excluded if they were pregnant or lactating, were allergic to hydrogel, had grossly oedematous legs, or were taking anticoagulants (contraindicated with larval therapy).

After consenting to the trial, participants were randomised to receive either loose larvae (Zoobiotic; Bridgend, Wales), bagged larvae (Biomonde; Barsbüttel, Germany), or hydrogel (Purilon; Coloplast, Denmark), with nurses using a remote, telephone randomisation service provided by York Trials Unit (allocation was therefore fully concealed). Randomisation was done using permuted blocks with stratification by trial centre and ulcer area ($\leq$5 cm^2 or >5 cm^2). A computer programmer, who was not involved in the data analysis, created the randomisation program using randomly permuted blocks with block sizes of three and six.

Interventions

Nurses were encouraged to consider all participants for compression and to use four layer bandaging unless contraindicated by ankle brachial pressure index or patient tolerance.

We used sterile *Lucilia sericata* larvae. The number of larvae required for each application was determined from manufacturers' guides. Larvae were left on the ulcer for three or four days, and nurses could assess the participant during this period. Participants could not receive compression bandaging while larvae were in situ. If further larval therapy was required on removal of the dressing, hydrogel and the participant's usual bandage were applied while more larvae were ordered.

Participants in the control group received hydrogel covered with a knitted viscose dressing as well as compression depending on the ankle brachial pressure index and patient tolerance. Frequency of application was decided by the treating nurse.

The randomised treatment was applied in the debridement phase: this ended either when debridement occurred or when treatment was stopped before debridement (classified as withdrawal

from trial treatment). In the phase after debridement, participants received a standard knitted viscose dressing with or without compression. The maximum length of follow-up was 12 months, although some participants who were randomised towards the end of recruitment had follow-up of between six and 12 months. We stopped collecting routine clinical data for participants whose reference ulcer had healed but asked them to continue completing questionnaires on quality of life and use of resources.

Outcome measurements

The primary outcome was time to complete healing of the reference ulcer. Ulcer healing was defined as complete epithelial cover in the absence of a scab (eschar), which was assessed by the nurse with independent corroboration by another nurse one week later. In the event of disagreement, treatment continued until agreement was reached on healing status. Nurses took digital photographs weekly for six months and then monthly. These were assessed centrally to ascertain healing status by two independent assessors, masked to treatment group.

Secondary outcomes were time to debridement of the ulcer, health related quality of life, microbiology (bacterial load and MRSA), adverse events, and ulcer related pain. Debridement was defined as a cosmetically clean wound. Nurses recorded the date a wound had debrided. Debridement status was also assessed by masked independent assessors using digital photographs. We used the SF-12, previously found to be sensitive to changes in the healing status of venous ulcers, to measure participants' perceptions of health related quality of life both at the baseline assessment and at three, six, nine, and 12 months.

Microbiological swabs were taken at baseline, after removal of each trial debridement treatment during the first month (if the ulcer debrided within one month then weekly until one month), and then monthly until healing or completion of the trial. Laboratory analysis, blind to treatment, measured total bacterial load (10^x copies/ml) and the presence or absence of MRSA.

We classed adverse events as serious or non-serious. Some events were always classified as serious (death, life threatening event, admission to hospital, persistent or significant disability or incapacity); the seriousness of other events (for example, infection and deterioration of the wound) was judged by the treating nurse. Health professionals indicated whether or not they believed the event was related to trial treatment. On the basis of reports in the literature, we established a list of possible treatment related adverse events a priori (pressure damage, maceration, excoriation and infection ulcer related pain, ulcer deterioration).

Participants recorded ulcer related pain over the past 24 hours on a visual analogue scale at baseline and at first removal of the debridement treatment. The scale ranged from no pain (0 mm) to worst pain imaginable (150 mm).

Discussion

We found no evidence that a phase of treatment with loose or bagged larvae reduces the time to healing of leg ulcers compared with hydrogel. The median healing times (236 days for the larvae groups and 245 days for the hydrogel group) were longer than in our previous trial, where the median time to healing with four layer bandaging was 92 days and with short stretch bandaging was 126 days. The most likely explanation for the increased healing time in the current trial is that we restricted eligibility to the trial to patients with sloughy and necrotic leg ulcers and ulcers associated with more arterial disease than in the previous study. We also found no evidence of a difference in health related quality of life or bacterial load.

Our findings do, however, indicate that larvae are a more effective debriding agent than hydrogel. This is the first report of pain associated with larval therapy in a large number of patients with leg ulcers, with a control group for comparison. Pain reported in the 24 hours before removal of the first larvae treatment was considered related to the procedure and was probably transient and did not seem to impact on the health related quality of life measurements made at three monthly intervals.

The low rate of MRSA identified in these mainly community dwelling patients with leg ulcers is welcomed and contrasts with previous reports. We also showed that MRSA can be eradicated from leg ulcers irrespective of whether larval therapy is used.

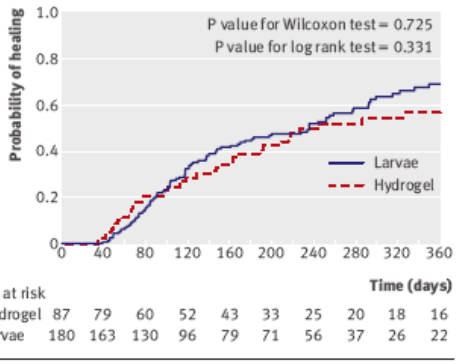

Fig 2| Kaplan Meier plot of time to ulcer healing after larval therapy (loose and bagged larvae arms combined) compared with hydrogel

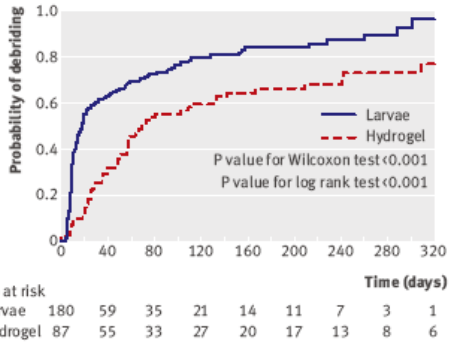

Fig 3| Kaplan Meier plot of time to debridement of ulcer using larvae (loose and bagged combined) compared with hydrogel

Strengths and limitations of study

We believe that this is the first randomised controlled trial to investigate the effect of larval therapy on wound healing and we used blinded outcome assessment to protect against observer bias. Although trial evidence is limited, there are several non-randomised controlled trials that led to the promotion of larval therapy as a clinically effective treatment; "effective" variously defined as the promotion of healing, promotion of debridement, reduction in number of micro-organisms in the wound, and reduction of MRSA specifically. The present trial provides a more robust evidence base to explore these issues.

As we did not investigate debridement as a longer term outcome we were unaware of how many ulcers that did debride remained debrided. Furthermore, although the current study is the first randomised controlled trial we have identified to investigate and publish data on the antimicrobial action of larval therapy, we also recognise the limitations of the methods used. We only investigated an association between larval therapy and total bacterial load. Beyond identification of MRSA we did not have the resources to carry out qualitative investigation of bacterial flora so can not draw any conclusions about the impact of larval therapy on other species.

Finally, as with many randomised controlled trials, recruitment of sufficient numbers of eligible patients was a challenge and we did not reach our initial sample size despite an extension in time and funding. The reasons for this are probably complex. Anecdotally, nurses thought there were fewer patients with leg ulcers than previously, attributing this to an increased use of compression bandaging. Secondly, fewer ulcers than we originally anticipated were sloughy. Indeed the main single reason for exclusion of patients from the trial was ulcers not containing sufficient slough. Since this is a prerequisite for using larval therapy, our experience suggests that doing a larger trial in the United Kingdom would be challenging.

Possible explanations and implications for clinicians and policymakers

We found no evidence to recommend the routine use of larval therapy on sloughy leg ulcers to speed up healing or reduce bacterial load. If debridement in itself is a goal of treatment, such as before skin grafting or other surgery, then larval therapy should be considered; however, it is associated with significantly more pain than hydrogel. Future treatment decisions should be fully informed by the finding that there is no evidence of an impact on healing time.

Unanswered questions and future research

The present study supports the view that larval therapy is an effective debriding agent. However, the study raises uncertainty about the role of debridement in the care of leg ulcers. Although debridement is viewed as an important part of preparation of the wound bed, data describing the relation between debridement and healing are sparse. Research is required to explore the relation between debridement, healing, and microbiology as well to better understand the value of debridement as an outcome from the patient's perspective.