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RESEARCH

Larval therapy for leg ulcers (VenUS II): randomised controlled trial

Jo C Dumville,[1] Gill Worthy,[1] J Martin Bland,[1] Nicky Cullum,[1] Christopher Dowson,[2] Cynthia Iglesias,[1] Joanne L Mitchell,[3] E Andrea Nelson,[4] Marta O Soares,[1] David J Torgerson,[1] on behalf of the VenUS II team

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[1]Department of Health Sciences, University of York, York YO10 5DD
[2]Biological Sciences, University of Warwick
[3]Micropathology Ltd, Coventry
[4]School of Healthcare, University of Leeds
Correspondence to: Jo C Dumville
jd34@york.ac.uk

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ABSTRACT

Objective To compare the clinical effectiveness of larval therapy with a standard debridement technique (hydrogel) for sloughy or necrotic leg ulcers.

Design Pragmatic, three armed randomised controlled trial.

Setting Community nurse led services; hospital wards; hospital outpatient leg ulcer clinics in urban and rural settings, United Kingdom.

Participants 267 patients with at least one venous or mixed venous and arterial ulcer with at least 25% coverage of slough or necrotic tissue, and an ankle brachial pressure index of 0.6 or more.

Interventions Loose larvae, bagged larvae, and hydrogel.

Main outcome measures The primary outcome was time to healing of the largest eligible ulcer. Secondary outcomes were time to debridement, health related quality of life (SF-12), bacterial load, presence of meticillin resistant *Staphylococcus aureus*, adverse events, and ulcer related pain (visual analogue scale, from 0 mm for no pain to 150 mm for worst pain imaginable).

Results Time to healing was not significantly different between the loose or bagged larvae group and the hydrogel group (hazard ratio for healing using larvae *v* hydrogel 1.13, 95% confidence interval 0.76 to 1.68; P=0.54). Larval therapy significantly reduced the time to debridement (2.31, 1.65 to 3.2; P<0.001). Health related quality of life and change in bacterial load over time were not significantly different between the groups. 6.7% of participants had MRSA at baseline. No difference was found between larval therapy and hydrogel in their ability to eradicate MRSA by the end of the debridement phase (75% (9/12) *v* 50% (3/6); P=0.34), although this comparison was underpowered. Mean ulcer related pain scores were higher in either larvae group compared with hydrogel (mean difference in pain score: loose larvae *v* hydrogel 46.74 (95% confidence interval 32.44 to 61.04), P<0.001; bagged larvae *v* hydrogel 38.58 (23.46 to 53.70), P<0.001).

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.

Trial registration Current Controlled Trials ISRCTN55114812 and National Research Register N0484123692.

INTRODUCTION

Larval therapy is used to promote wound debridement and has also been suggested to stimulate wound healing,[1] reduce bacterial load,[2] and eradicate meticillin resistant *Staphylococcus aureus*.[3] However, the treatment has been evaluated in just one published randomised controlled trial, which included only 12 patients with venous leg ulcers and reported debridement and not healing.[4] We evaluated the effectiveness of larval therapy compared with a standard debridement treatment (hydrogel) in the treatment of leg ulcers, The economic evaluation is reported in the accompanying paper.[5]

METHODS

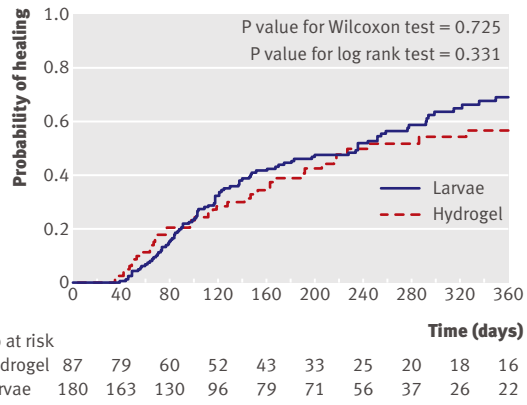
This was a pragmatic multicentre, randomised, open trial with equal randomisation, carried out in 22 centres in the United Kingdom from July 2004 to May 2007. Eligible participants had venous or mixed venous and arterial leg ulcers with at least 25% coverage by slough or necrotic tissue. We considered ulcers with an area of 5 cm^2 or less as eligible if they were non-healing (no change in area over preceding month). If a patient had multiple ulcers we chose the largest eligible ulcer as the reference lesion.

Participants were randomised to receive loose larvae (Zoobiotic; Bridgend, Wales), bagged larvae (Biomonde; Barsbüttel, Germany), or hydrogel (Purilon; Coloplast, Denmark). Randomisation was done by telephone, using permuted blocks with stratification by trial centre and ulcer area (≤5 cm^2 or >5 cm^2).

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, which were left in situ for three or four days; during which participants could not receive compression bandaging. Participants in the control group received hydrogel covered with a



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

knitted viscose dressing and compression depending on the ankle brachial pressure index and patient tolerance.

Allocated treatment was applied in the debridement phase. 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.

Outcome measurements

The primary outcome was time to healing of the reference ulcer, defined as complete epithelial cover in the absence of a scab, which was assessed by the nurse and independently corroborated by another nurse one week later. Nurses took photographs of the ulcer weekly for six months and then monthly. These were assessed for healing status by two independent assessors, masked to treatment.

Secondary outcomes were time to debridement, health related quality of life, 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, and blinded assessors checked photographs to judge whether complete debridement had occurred. We used the SF-12[6] to measure participants' perceptions of health related quality of life at baseline and at three, six, nine, and 12 months.

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 the trial ended. Laboratory analysis, blinded to treatment, measured total bacterial load and MRSA.

We classed adverse events as serious (for example, life threatening event, admission to hospital) or non-serious. 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.

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

Statistical analysis

We compared time to debridement and time to healing between the groups using a log rank test. These treatment effects were explored in a Cox proportional hazards model including randomisation stratification factors (centre, baseline ulcer area) as well as prognostic variables (duration of ulcer and ulcer type: ankle brachial pressure index ≥0.8 and high compression or lower or no compression; ankle brachial pressure index 0.6-0.8). We decided a priori that if there was no evidence of a difference between loose and bagged larvae groups we would present the hazard ratios and 95% confidence intervals for larvae groups combined compared with hydrogel.

For each participant we calculated the physical and mental component scores of the SF-12. The standardised areas under the curve[7] were reported for the larvae and hydrogel groups and compared using a Wilcoxon rank sum test. Values were compared with those of age specific norms, available for the United States.[8]

Data on bacterial load were log transformed. We used a repeated measures regression model to compare changes in bacterial load over time between the groups. Time of swabbing was a continuous measure and we included a quadratic term to test if the effects of time were non-linear. We considered treatment, time, baseline ulcer area, ulcer type, and duration of ulcer as fixed effects and participants as random effects. The interaction between treatment and time was also assessed. We analysed bacterial load to the end of the trial and to the end of the debridement phase.

We used Fisher's exact test to compare the proportion of participants (positive for MRSA at baseline) with MRSA eradicated by the end of the debridement phase between larvae and hydrogel groups. This was repeated for the proportion of participants who were negative for MRSA at baseline but who tested positive later.

Using a negative binomial model and adjusting for the same covariates as the primary analyses we compared the numbers of adverse events in each participant between treatment groups. We also compared groups for ulcer related pain during the 24 hours before the first removal of the debridement treatment using linear regression and adjusting for baseline pain score, ulcer area, duration of ulcer, and ulcer type.

RESULTS

Overall, 267 of 1712 (15.6%) people with leg ulcers were randomised: 94 to loose larvae, 86 to bagged larvae, and 87 to hydrogel. See bmj.com for characteristics of the participants.

Time to healing did not differ between the groups (log rank test 1.00, df=2, P=0.62). In the adjusted analysis, as healing rates did not differ between the loose and bagged larvae arms (χ^2 0.19, df=1, P=0.66), results are presented for the larvae arms combined compared with hydrogel. The median time to healing in the larvae group was 236 days (95% confidence interval 147 to 292) and in

WHAT IS ALREADY KNOWN ON THIS TOPIC

Larvae are increasingly used to treat leg ulcers and are thought to stimulate healing, reduce bacterial load, and eradicate MRSA

Clinical evidence to support larval therapy comes from a small randomised controlled trial that did not follow patients to healing

WHAT THIS STUDY ADDS

Larval therapy significantly reduced the time to debridement of sloughy or necrotic leg ulcers compared with hydrogel

Larval therapy did not increase healing rates nor reduce bacterial load and was associated with significantly more ulcer related pain in the 24 hours before removal of the first treatment than with hydrogel

the hydrogel group was 245 days (166 to not estimable). The figure shows the survival curve for time to healing.

The hazard ratio from the adjusted analysis for larvae compared with hydrogel was 1.13 (95% confidence interval 0.76 to 1.68, P=0.54), indicating a slightly increased likelihood of healing in the larvae group, although this was not statistically significant.

Time to debridement differed significantly between the three groups (25.38, df=2, log rank test P<0.001). The median time to debridement with loose larvae was shorter (14 days, 95% confidence interval 10 to 17) than with bagged larvae (28 days, 13 to 55) and with hydrogel (72 days, 56 to 131). When loose and bagged larvae were compared in the adjusted analysis, however, the difference in time to debridement was not significant (χ^2 1.52, df=1, P=0.22).

The rate of debridement at any time in either larvae groups was about twice that of the hydrogel group (hazard ratio for combined larvae group compared with hydrogel 2.31, 95% confidence interval 1.65 to 3.24, P<0.001).

The mean baseline physical component score for the combined larvae group was 33.3 (SD 11.4) and for the hydrogel group was 35.9 (SD 11.5). These values were low compared with the 37.9 (SD 11.16) for norm based scores of people aged 75 and over in the US. The mean baseline mental component score for the combined larvae group was 46.9 (SD 12.3) and for the hydrogel group was 47.2 (SD 11.0), compared with 50.4 (11.66) for the general US population. The physical component summary scores did not differ between the groups (median area under the curve: 0.4 for combined larvae, −0.5 for hydrogel, P=0.25), indicating no evidence of a difference between them (see bmj.com). The result for the mental component summary score was −0.8 for combined larvae, −0.7 for hydrogel, P=0.95 (see bmj.com).

The average log bacterial count at baseline was 6.5 (about 3.1×10^6 copies/ml) and was similar across the groups. Data from swabs showed no evidence of a difference in bacterial load over time between the combined larvae and the hydrogel groups (difference in means (larvae minus hydrogel) −0.06, 95% confidence interval −0.24 to 0.12, P=0.75).

The prevalence of MRSA at baseline was low, with only 6.7% of participants (18/267) having a positive swab at baseline: seven participants allocated to loose larvae, five allocated to bagged larvae, and six allocated to hydrogel. Of these, MRSA was eradicated during the debridement phase in, respectively, 57.1% (4/7), 100% (5/5), and 50% (3/6). There was no evidence of a difference between the combined larvae and the hydrogel groups (75% (9/12) *v* 50% (3/6); P=0.34). The number of participants who were negative for MRSA at baseline but positive at one or more follow-up assessments did not differ between the combined larvae and the hydrogel groups (7.1% (12/168) *v* 2.5% (2/81); Fisher's exact test P=0.16).

In total, 131 participants had 340 adverse events. Of these, 13.8% were classed as serious, corresponding to 14.6% events with loose larvae, 13.5% with bagged larvae, and 13.5% with hydrogel.

The mean ulcer related pain scores with larvae were about double those with hydrogel (see bmj.com). After adjustment, significantly more pain was experienced by participants in both larvae groups (P<0.001) than in the hydrogel group.

DISCUSSION

A phase of treatment with loose or bagged larvae did not reduce time to healing of leg ulcers compared with hydrogel. We also found no evidence of a difference in health related quality of life or bacterial load. Our findings do indicate that larvae are a more effective debriding agent than hydrogel.

This is the first report of pain associated with larval therapy, 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 therefore 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 is welcomed and contrasts with previous reports.[9 10] We also showed that MRSA can be eradicated from leg ulcers irrespective of treatment type. One limitation was that we only investigated an association between larval therapy and total bacterial load. Beyond identification of MRSA we did not investigate other bacterial flora.

We investigated the effect of larval therapy on wound healing and 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,[11-15] with "effective" variously defined.

Finally, we did not reach our initial sample size. The reasons may be complex. Anecdotally, nurses thought there were fewer patients with leg ulcer than previously, attributing this to an increased use of compression bandaging. Secondly, fewer ulcers than we originally anticipated were sloughy.

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, then larval therapy should

be considered; however, it is associated with significantly more pain than hydrogel.

We thank the participants for taking part in the trial; the research nurses, tissue viability teams, district nurses, and hospital outpatient staff for recruiting participants and completing the trial documentation; the principal investigators at each site for coordinating recruitment of the participants; members of the trial steering committee (Su Mason (independent chair), Mike Campbell, and Francine Cheater); and members of the data monitoring and ethics committee (Keith Abrams (chair), Michelle Briggs, and Alun Davies) for overseeing the study. The VenUS II collaborators (current and past) are: Una Adderley, Jacqui Ashton, Gill Bennett, JMB, Anne Marie Brown, Sue Collins, Ben Cross, NC, Val Douglas, CD, JCD, Andrea Ellis, Caroline Graham, Christine Hodgson, Gemma Hancock, Shervanthi Homer-Vanniasinkam, CI, June Jones, Nicky Kimpton, Dorothy McCaughan, Elizabeth McGinnis, Jeremy Miles, JLM, Veronica Morton, EAN, Sue O'Meara, Angie Oswald, Emily Petherick, Ann Potter, Pauline Raynor, Linda Russell, Jane Stevens, MS, Nikki Stubbs, DJT, Kath Vowden, Peter Vowden, Michael Walker, Shernaz Walton, Val Wadsworth, Margaret Wallace Judith Watson, Anne Witherow, and GW.

Contributors: See bmj.com.

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Competing interests: None declared.

Ethical approval: This study was approved by the West Midlands multicentre research ethics committee and local ethics committees.

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Cost effectiveness analysis of larval therapy for leg ulcers

Marta O Soares,[1] Cynthia P Iglesias,[1] J Martin Bland,[1] Nicky Cullum,[1] Jo C Dumville,[1] E Andrea Nelson,[2] David J Torgerson,[1] Gill Worthy,[1] on behalf of the VenUS II team

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[1]Department of Health Sciences, University of York, York YO10 5DD
[2]School of Healthcare, University of Leeds, UK

Correspondence to: M O Soares
ms602@york.ac.uk

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ABSTRACT

Objective To assess the cost effectiveness of larval therapy compared with hydrogel in the management of leg ulcers.

Design Cost effectiveness and cost utility analyses carried out alongside a pragmatic multicentre, randomised, open trial with equal randomisation.

Population Intention to treat population comprising 267 patients with a venous or mixed venous and arterial ulcers with at least 25% coverage of slough or necrotic tissue.

Interventions Patients were randomly allocated to debridement with bagged larvae, loose larvae, or hydrogel.

Main outcome measure The time horizon was 12 months and costs were estimated from the UK National Health Service perspective. Cost effectiveness outcomes are expressed in terms of incremental costs per ulcer-free day (cost effectiveness analysis) and incremental costs per quality adjusted life years (cost utility analysis).

Results The larvae arms were pooled for the main analysis. Treatment with larval therapy cost, on average, £96.70 (€109.61; $140.57) more per participant per year (95% confidence interval −£491.9 to £685.8) than treatment with hydrogel. Participants treated with larval therapy healed, on average, 2.42 days before those in the hydrogel arm (95% confidence interval −0.95 to 31.91 days) and had a slightly better health related quality of life, as the annual difference in QALYs was 0.011 (95% confidence interval −0.067 to 0.071). However, none of these differences was statistically significant. The incremental cost effectiveness ratio for the base case analysis was estimated at £8826 per QALY gained and £40 per ulcer-free day. Considerable uncertainty surrounds the outcome estimates.

Conclusions Debridement of sloughy or necrotic leg ulcers with larval therapy is likely to produce similar health benefits and have similar costs to treatment with hydrogel.

Trial registration Current Controlled Trials ISRCTN55114812 and National Research Register N0484123692.

INTRODUCTION

A common belief is that necrotic tissue and slough might interfere with wound healing, although no strong evidence supports this theory.[1-3] Larval therapy has been proposed as a potentially effective and cost effective method for debridement and is thought to promote healing. Compared with hydrogel (standard treatment), each application of larvae is expensive (£58 for loose larvae, £98.79 for bagged larvae, £1.55 for hydrogel) and more consultations with nurses are likely to be required up to debridement.

We carried out an economic evaluation alongside a large multicentre randomised controlled trial to investigate the cost effectiveness of larval therapy compared with hydrogel in patients with sloughy or necrotic venous and mixed venous and arterial leg ulcers. The clinical results are published in an accompanying paper.[4]

METHODS

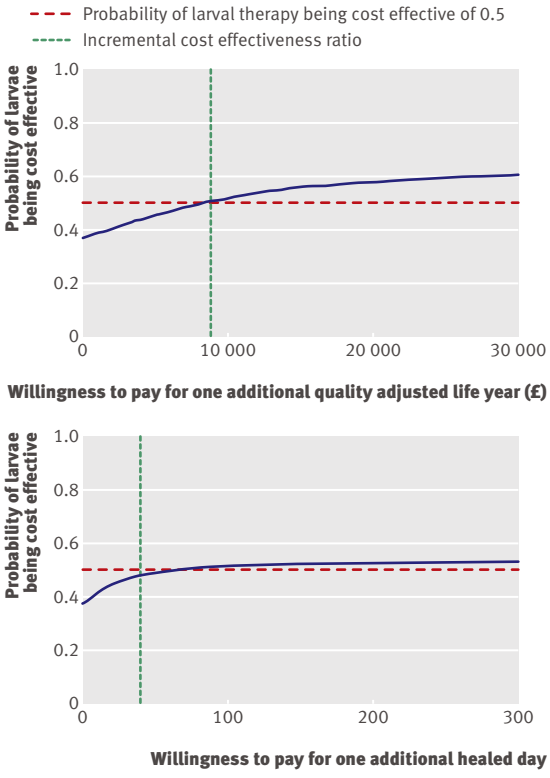
Patients with venous or mixed venous and arterial leg ulcers were eligible for recruitment if one of the ulcers had at least 25% surface coverage with slough or necrotic tissue. Participants were randomised to hydrogel, loose larvae, or bagged larvae. Larvae were left in situ for three or four days, during which time the patients received nursing care for wound management. On removal of the larvae the treating nurse assessed whether a further application was required. We refer to the application of treatment until debridement or the discontinuation of treatment as the debridement phase. Participants did not receive compression during larval therapy. This trial design therefore relates to the pragmatic question of whether the benefits of larval therapy outweigh the disbenefits of going without compression during larval therapy.

Economic analysis

We used patient level data collected within a randomised controlled trial (VenUS II). Intention to treat analyses compared incremental costs with incremental ulcer-free days (cost effectiveness analysis) and incremental quality adjusted life years (cost utility analysis). Time to healing was the outcome measure in the cost effectiveness analysis.

The perspective for the economic evaluations was that of the NHS and Personal Social Services.[5] The year of pricing was 2006. The time horizon was 12 months after recruitment, and consequently we discounted neither costs nor health benefits.

As decided a priori in the clinical analysis, if evidence of a statistically non-significant difference in debridement time between loose and bagged larvae was found, data from both groups would be pooled. The incremental economic analysis therefore considered the combined group.



Base case analysis cost effectiveness acceptability curve

Resource use and unit costs

We collected data on use of resources from nurse completed and participant completed questionnaires. Information on numbers of loose and bagged larvae and hydrogel applications was recorded by nurses at each consultation. Unit costs for debriding agents were obtained from the *British National Formulary* and larvae suppliers.

Data on contacts with nurses and doctors were available from both nurses and participants. Nurse reported data were collected for only the reference ulcer, and participants' reported data for all ulcers and ulcer related conditions. Participants with several ulcers continued recording healthcare resource use irrespective of the healing status of the reference ulcer, and these data were used in the base case analysis. Hospital consultations were costed on an outpatient basis (see bmj.com).

The type of compression therapy was recorded at each visit and the costs estimated as the arithmetical average cost for commercially available systems.[4] Other dressings and treatments were assumed to be used similarly across treatment arms.[6]

Health outcomes

Health benefit was measured in terms of ulcer-free days and quality adjusted life years (QALYs). Time to healing of the reference ulcer was recorded by nurses and independently ascertained from photographs by blinded investigators.[4] Health related quality of life data (EQ-5D[7]) were collected at baseline and at three, six, nine, and 12 months. Utility scores were calculated using an independent predefined algorithm.[8] Thus

time lived in perfect health has a weight of 1, which decreases as health becomes impaired. Quarterly QALYs were calculated by applying individual's utility weights to survival time using the area under the curve approach,[9 10] which was defined by linearly interpolating the utility scores measured over time.

Statistical analysis

Estimates of expected cost and health benefit were reported for larval therapy (pooled data) and hydrogel. For completeness we present descriptive measures of costs and health benefits for each of the three trial arms.

We used inverse probability weighting[11-13] to estimate the mean time to healing, costs, and QALYs, accounting for the censored nature of these data.[14] The weights were evaluated as the inverse of the Kaplan Meier estimator of censoring probability. For QALYs and cost estimation, we partitioned the time horizon in quarterly intervals through the weighted regression mean cost, and QALYs were estimated within each interval and then summed across intervals to estimate mean total costs and QALYs.

Linear regression was used to adjust the estimates for type of ulcer, duration of ulcer (logarithmic), ulcer area (logarithmic), and centre (aggregating centres with fewer than 10 participants). We included baseline EQ-5D scores as a covariate in the estimation of QALYs.[9]

We calculated 95% confidence intervals for differential costs and effectiveness using non-parametric bootstrap estimates (bias corrected).[15] For each bootstrap resample we obtained adjusted estimates of expected total costs and effectiveness measures.

A treatment strategy can be considered cost effective only if the decision maker's willingness to pay for an additional unit of health benefit is equal to or greater than the incremental cost effectiveness ratio. Nevertheless, this cost effectiveness decision is uncertain because expected costs and effectiveness are estimated under conditions of uncertainty. We explored this uncertainty using cost effectiveness planes and acceptability curves.[16]

RESULTS

Overall, 267 people were recruited: 94 were allocated to loose larvae, 86 to bagged larvae, and 87 to hydrogel. Randomised treatments were administered to 88 (94%), 82 (95%), and 78 (90%) participants, respectively. Mean follow-up time was 171 days (167 days for loose larvae group, 170 days for bagged larvae group, and 175 days for hydrogel group).

Resource use

Participants allocated to larval therapy received their first application about three days later than those allocated to hydrogel, owing to the need to order the larvae (see bmj.com). Participants in either larval therapy arm received on average 1.45 applications before the treatment was discontinued or data were censored compared with on average 9.2 applications in the hydrogel arm. Nineteen participants never received the allocated treatment. The duration of trial treatment was, on average, 30 days longer in the hydrogel arm than in the larvae arms (43 *v* 12 days).

The average numbers of total consultations with healthcare professionals during follow-up were similar across groups (59 for loose larvae, 56 for bagged larvae, and 61 for hydrogel), with most visits being ulcer related (81% overall, 47/58; see bmj.com). Nurse consultations accounted for 71% of the total number of healthcare consultations (42/59).

The use of high and low compression bandaging was similar across the three arms (see bmj.com)—compression was received by 87% of participants (82/94) in the loose larvae arm, 91% (78/86) in the bagged larvae arm, and 93% (81/87) in the hydrogel arm.

Total costs

The average estimated cost of the trial treatment per application was: loose larvae £71.70 (SD £13.40), bagged larvae £111.90 (SD 33.6), and hydrogel £1.50 (SD 0).

The mean total unadjusted costs incurred by participants was £1833 (SD £1978) for loose larvae, £1696 (SD £1948) for bagged larvae, and £1596 (SD £1861) for hydrogel. The cost of nurse and hospital visits was the major driver of total costs; representing 85% for loose larvae, 77% for bagged larvae, and 82% of the total unadjusted costs for hydrogel. Half of the mean incurred costs observed during the trial (available case analysis) were incurred during the first three months of follow-up in all arms. The analysis adjusted for censoring, baseline imbalances, and stratification variables shows that treatment with larvae costs, on average, £96.70 more per participant per year (95% confidence interval −£491.90 to £685.80) than treatment with hydrogel (see bmj.com). This difference was not statistically significant.

Health outcomes

On average and after adjustment for baseline imbalances and stratification variables, participants treated with larval therapy healed 2.42 days before those in the hydrogel arm. However, this difference was not statistically significant (95% confidence interval −40.95 days to 31.91 days; see bmj.com).

The adjusted results show that patients in the larval therapy arms had, on average, a slightly better quality of life than those in the hydrogel arm (annual difference in QALYs 0.011, 95% confidence interval −0.067 to 0.071; see bmj.com).

Cost effectiveness and associated uncertainty

The incremental cost effectiveness ratio associated with use of larval therapy was estimated at £8826 per QALY gained and £40 per ulcer-free day. The point estimates of cost and effect differences were small relative to their standard error, indicating considerable uncertainty associated with the decision to adopt larval therapy (see bmj.com).

Despite the point estimate for the incremental cost-utility ratio (£8826) being below the £30 000 per QALY that is generally accepted as being a "threshold"

WHAT IS ALREADY KNOWN ON THIS TOPIC

Larval therapy, a traditional approach to wound management, is widely used on leg ulcers

Only one randomised trial with 12 participants has been carried out previously and did not measure ulcer healing or do a full cost effectiveness analysis

WHAT THIS STUDY ADDS

Larval therapy for the debridement of sloughy or necrotic venous or mixed aetiology leg ulcers is likely to have similar cost effectiveness to hydrogel

Healthcare decision makers should generally be indifferent when recommending between these two treatments

The choice of treatment may then be driven by patients' wishes and experiences of pain with larvae

of cost effectiveness by the National Institute for Health and Clinical Excellence, considerable uncertainty surrounds this estimate. The cost effectiveness acceptability curve (figure), plotted for a range of willingness to pay thresholds (cost per QALY), suggests that in the base case analysis the probability of larvae being cost effective in relation to hydrogel never exceeds 63%.

DISCUSSION

Our base case analysis indicates that, compared with hydrogel, larval therapy confers a small health benefit for people with leg ulcers, as measured by QALYs and time to healing, at a minor additional cost to the NHS. The incremental cost effectiveness ratio for the base case analysis was estimated at £8826 per QALY gained and £40 per ulcer-free day. Yet our non-parametric confidence intervals indicated a high level of uncertainty associated with the differential cost, effectiveness, and cost effectiveness of larval therapy compared with hydrogel. The spread of points on the cost effectiveness plane (see bmj.com) was almost uniform over the four quadrants, suggesting that the nature of the uncertainty associated with our results is such that larval therapy is likely to be as costly and as effective as hydrogel.

Debridement and health related quality of life

The impact of larval therapy on health related quality of life is unclear. As a consequence of the high levels of morbidity in patients with leg ulcers, it could be argued that generic health related quality of life instruments might not capture the benefits of ulcer treatments. Previous work, however, showed that both the SF-12 and EQ-5D are sensitive to, and thus able to measure, changes in healing status of patients with venous leg ulcer.[17] Although debridement was more rapid with larval therapy, measurement of its effect on health related quality of life might have been hindered by some factors. Health related quality of life data were collected at quarterly intervals whereas the median time for debridement in the larvae groups was between 14 and 28 days[10]; this time gap might have interfered with the instrument's ability to capture any small changes in health related quality of life.

Data characteristics

An important characteristic of our dataset was the high proportion of censored data. Heavy censoring is not unusual in studies on patients with high morbidity and frequent transfers between hospital and community healthcare settings. Baseline health related quality of life scores indicated a higher than average level of morbidity among the population under evaluation, which may account for more than 40% of participants failing to complete the health related quality of life questionnaires at the final follow-up. Inverse probability weighting methods were used to account for this important feature of our data in the estimation of mean health benefits and costs.

In this cost effectiveness analysis, healing was the event of interest; individuals lost to follow-up were censored as were those who died. As healing cannot occur after death, censoring in such cases may conflict with the assumption of non-informative censoring, common to most methods of survival analysis.

Strengths and weaknesses

This is the first full economic evaluation alongside a randomised controlled trial evaluating the value for money of a single phase of larval therapy compared with hydrogel for the debridement and healing of sloughy or necrotic venous or mixed aetiology leg ulcers.

While our findings have strong external validity for the UK NHS, the applicability of these results to other settings worldwide may require further consideration. Variations on the use of debriding agents may have an impact on the cost effectiveness of these treatments.

Conclusions

One phase of larval therapy used until initial debridement of leg ulcers is likely to produce a similar level of health benefit at a similar cost to hydrogel. It could be argued that decision makers should be indifferent when recommending these two therapies or that the decision should be driven by the goal of treatment. The choice of treatment may then be driven by patients' wishes and experiences of pain with larvae.

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Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients

Susan O'Meara,[1] Jayne Tierney,[2] Nicky Cullum,[1] J Martin Bland,[1] Peter J Franks,[3,4] Trevor Mole,[5] Mark Scriven[6]

EDITORIAL by Grey and colleagues
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[1]Department of Health Sciences, University of York, York YO10 5DD
[2]Meta-analysis Group, MRC Clinical Trials Unit, London NW1 2DA
[3]Centre for Research and Implementation of Clinical Practice, London SW15 5ES
[4]Faculty of Medicine, Division of Nursing and Healthcare, University of Glasgow, Glasgow G12 8LW
[5]Smith and Nephew Wound Management, Hull HU3 2BN
[6]Department of Vascular Surgery, Birmingham Heartlands Hospital, Birmingham B9 5SS
Correspondence to: S O'Meara
smo4@york.ac.uk

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ABSTRACT

Objective To compare the effectiveness of two types of compression treatment (four layer bandage and short stretch bandage) in people with venous leg ulceration.
Design Systematic review and meta-analysis of patient level data.
Data sources Electronic databases (the Cochrane Central Register of Controlled Trials, the Cochrane Wounds Group Specialised Register, Medline, Embase, CINAHL, and National Research Register) and reference lists of retrieved articles searched to identify relevant trials and primary investigators. Primary investigators of eligible trials were invited to contribute raw data for re-analysis.
Review methods Randomised controlled trials of four layer bandage compared with short stretch bandage in people with venous leg ulceration were eligible for inclusion. The primary outcome for the meta-analysis was time to healing. Cox proportional hazards models were run to compare the methods in terms of time to healing with adjustment for independent predictors of healing. Secondary outcomes included incidence and number of adverse events per patient.
Results Seven eligible trials were identified (887 patients), and patient level data were retrieved for five (797 patients, 90% of known randomised patients). The four layer bandage was associated with significantly shorter time to healing: hazard ratio (95% confidence interval) from multifactorial model based on five trials was 1.31 (1.09 to 1.58), P=0.005. Larger ulcer area at baseline, more chronic ulceration, and previous ulceration were all independent predictors of delayed healing. Data from two trials showed no evidence of a difference in adverse event profiles between the two bandage types.
Conclusions Venous leg ulcers in patients treated with four layer bandages heal faster, on average, than those of people treated with the short stretch bandage. Benefits were consistent across patients with differing prognostic profiles.

INTRODUCTION

Compression bandaging is thought to assist healing of venous leg ulcers by reducing distension in the leg veins and accelerating venous blood flow.[1] A previous systematic review of published trial level data concluded that compression was more effective in healing venous leg ulcers than no compression, multi-layered systems were more effective than single layer systems,

and high compression was more effective than low compression, but no clear differences in effectiveness were detected between different types of high compression.[2]

The four layer bandage (an elastic system), which is the standard compression treatment in the United Kingdom, comprises orthopaedic wool, crepe bandage, elastic bandage, and a final cohesive retaining layer. All layers are applied from toes to knee and normally require weekly renewal but can be changed more often if necessary. The short stretch system, standard treatment in mainland Europe and Australia, is an inelastic bandage. An orthopaedic wool layer is covered by the bandage applied at full stretch to create a rigid casing around the limb that generates resistance against calf muscles and other tissues with reapplication every few days.[1] The short stretch bandage has the advantage of being washable and reusable.[3] The four layer bandage is designed to be discarded after a single use.

We carried out a systematic review and meta-analysis based on individual patient data to compare the effects of four layer bandage and short stretch bandage on time to healing of venous leg ulcers, taking account of prognostic factors.

METHODS

Randomised controlled trials of four layer bandage compared with short stretch bandage for the treatment of venous leg ulcers were eligible for inclusion. See bmj.com for databases searched. All searches were updated in March 2008. We examined the reference lists of eligible trials and asked trialists for details of other trials. Two reviewers (SO'M and NC) independently decided on study selection with disagreements resolved by discussion.

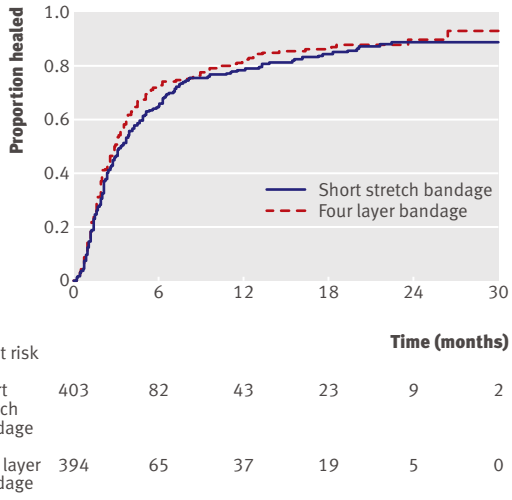
Data collection and end points

We established contact with authors of all relevant trials. We asked trialists to provide anonymised baseline and outcome data for each randomised patient, including those excluded from their own analyses, to maintain randomised groups and to provide as complete a dataset as possible for the meta-analysis. See bmj.com.

Time to healing was defined as the time from the date of randomisation to the date of healing, with healing defined as complete epithelialisation of the reference wound. Wounds were examined at least once a week in all trials. Data for patients with ulcers not healing within the trial period were censored on the date of last follow-up.

Statistical analysis

The patient was both the sampling unit and the unit of analysis.[4] In cases where patients had multiple wounds included in the trial, we selected the largest for inclusion in the meta-analysis. Analyses were undertaken on an intention to treat basis.



No at risk						
Short stretch bandage	403	82	43	23	9	2
Four layer bandage	394	65	37	19	5	0

Hazard ratio plot for time to healing with pooled and individual estimates adjusted for baseline ulcer area and ulcer duration

The primary outcome was time to healing. We performed a preliminary (unadjusted) analysis by generating non-stratified Kaplan-Meier survival curves for both treatment groups. The dependent variable was time to healing in days, the event was a healed ulcer, and the factor was bandage type.

Next, we generated a Cox proportional hazards model with time to healing in days as the dependent variable, healing as the event, and bandage type as a covariate. This preliminary model did not include adjustment for baseline characteristics. The main preplanned analysis entailed a Cox proportional hazards model with additional covariates of sex, age, primary or recurrent ulceration, ulcer duration, ulcer area, ulcer diameter, appearance of wound bed, ulcer infection, ankle brachial pressure index, ankle circumference, ankle mobility, patient's mobility, and history of comorbidities—for example, deep vein thrombosis. We then used a backward elimination method to generate hazard ratio estimates of treatment effect. The model was extended to include tests of statistical interaction between type of bandage and baseline characteristics. To take account of any differences in healing rate between study centres, we entered centres into the model as strata; this also automatically included trials as strata.

To generate a forest plot showing the relative contribution of each trial to the meta-analysis, we derived individual trial estimates from the individual patient data using Cox regression with covariate adjustment as per the final model. These hazard ratio estimates were then combined to provide a visual display of the overall estimate of treatment effect. This secondary analysis allowed assessment of heterogeneity between trials, defined with the χ^2 test (cut off $<10\%$ for significance) and the I^2 statistic (threshold of $>50\%$).

Adverse events were defined as any adverse event or those considered by the original investigators to be related to the bandage. For each of these, we assessed

the effect of bandage type on the incidence of adverse events using the odds ratio. We compared the number of adverse events per patient for the two bandage systems using a weighted mean difference.

RESULTS

The search strategy retrieved 128 records of possible relevance. Of these, six trials were eligible for inclusion.[w1-w6] We could not retrieve data for one trial because all records had been destroyed.[w2]

We identified an additional eligible unpublished trial but data for this trial were no longer available. See bmj.com for details of all eligible trials and patients' characteristics for the five trials with available individual patient data (89.8% of known randomised patients). Prognostic factors were balanced across treatment groups for the meta-analysis dataset.

All five trials used adequate methods of randomisation and allocation concealment and all defined healing as complete epithelial cover of the ulcer site with non-blinded assessment by clinicians.[w3-w6]

The characteristics of patients included in this meta-analysis seemed generally representative and there was an adequate spread of data for prognostic baseline variables such as ulcer area and ulcer duration. Most patients were ambulant. Reported follow-up periods for trials ranged from three to 12 months. The overall median follow-up of patients who did not heal during the trial period was around 13 weeks.

Time to healing

Preliminary analysis

The median time to healing estimated from unstratified Kaplan-Meier survival analysis of all available patients (n=797) was 90 days for four layer bandage and 99 days for the short stretch bandage.

Main analysis

An initial Cox proportional hazards model based on all five trials (797 patients, 20/797 cases dropped) was generated with time to healing (days) as the dependent variable, healing as the event, study centres as strata, and bandage type as the only covariate. The result of this unadjusted analysis indicated no significant difference between bandage types: hazard ratio 1.15, 95% confidence interval 0.97 to 1.37; P=0.11.

The next Cox model (five trials, 797 patients, 75/797 cases dropped) included all significant covariates identified during univariate analyses. After backward elimination, the final model contained only those making a significant contribution: type of bandage, ulcer duration, and ulcer area (table). The hazard ratio for bandage type was 1.31 (1.09 to 1.58; P=0.005), suggesting an increased probability of healing of around 30% with the four layer bandage. There was significant evidence that larger ulcers (P<0.001) and ulcers of longer duration (P<0.001) predicted longer time to healing independently of one another and of treatment. The chance of healing was reduced by a factor of 0.44 for each 10-fold increase in area. We categorised baseline ulcer duration into ≤1month, >1-6 months, >6-12 months, and >12 months. The data suggest that the hazard of healing was reduced for each step up to a longer duration interval. We found no significant interactions between bandage and baseline ulcer area and bandage and ulcer duration. The figure illustrates the relative contribution of each trial to the meta-analysis (heterogeneity between trials: χ^2 test P=0.11, I^2=47.7%).

We re-ran the analysis on a subset of four trials (747 patients, 83/747 dropped) for which additional covariates were available (primary or recurrent ulceration and patient's mobility). The estimated hazard ratio for type of bandage was similar to the model based on five trials: 1.29, 1.06 to 1.57; P=0.011. The model suggested that larger ulcers (P<0.001), ulcers of longer duration (P<0.001), and previous ulceration (P<0.005) were independent predictors of longer time to healing.

Adverse events

Two trials provided data on adverse events.[w1 w6] For incidence of any type of adverse event, the pooled odds ratio (fixed effect) was 1.15 (95% confidence interval 0.81 to 1.62; P=0.43), providing no evidence of a difference between bandage types. The two trials differed in their definitions of bandage related adverse events. One trial coded events such as maceration, allergic reaction, eczema of periulcer skin, and infection as bandage related.[w1] Another trial, which compared primary dressings as well as bandages, attributed these events to the former.[w6] In view of this difference, we did not pool data. We estimated odds ratios for each trial individually and neither showed a

Final model based on five trials. Regression coefficients (β) with standard errors (SE) and hazard ratios (HR) with 95% confidence intervals

Variable	β (SE)	HR (95% CI)	P value
Bandage	0.27 (0.10)	1.31 (1.09 to 1.58)	0.005
Duration category (months):			
Overall	—	—	‹0.001
1.01-6.0 *v* 0-1	−0.12 (0.11)	0.89 (0.71 to 1.11)	0.293
6.01-12.0 *v* 0-1	−0.53 (0.19)	0.59 (0.40 to 0.85)	0.005
›12 *v* 0-1	−1.07 (0.19)	0.35 (0.24 to 0.50)	‹0.001
Log_e ulcer area	−0.36 (0.05)	0.70 (0.64 to 0.77)	‹0.001

WHAT IS ALREADY KNOWN ON THIS TOPIC

Venous leg ulceration is a common and recurring condition that imposes a considerable burden on patients and healthcare providers

Compression treatment is the first line treatment, commonly applied as a four layer bandage in the UK and short stretch bandage in other parts of the world

A systematic review of compression based on published trial reports did not detect a difference between the two methods in terms of the number of patients healed at fixed time points

WHAT THIS STUDY ADDS

When compared with the short stretch bandage, the four layer bandage increases the chance of healing by around 30% when independent prognostic factors are taken into account

The benefit of the four layer bandage is consistent across patients with differing prognostic profiles, independent predictors of delayed healing being larger baseline ulcer area, more chronic ulceration, and previous ulceration

significant difference between groups: 1.41 (0.94 to 2.11)[w1] and 0.78 (0.30 to 2.04).[w6]

Analysis of the number of all types of adverse event per patient did not show a difference between the two bandage systems. See bmj.com.

DISCUSSION

When compared with short stretch bandage, the four layer bandage increases the chance of healing by around 30% when independent prognostic factors are taken into account. The benefit of four layer bandaging is consistent across patients with differing prognostic profiles. The largest trial incorporated an economic analysis and concluded that the four layer system had lower costs with greater health benefits.[w1]

Findings from our meta-analysis are consistent with those from prognostic studies in suggesting that baseline ulcer area, ulcer duration, and recurrent ulceration are independent predictors of time to healing.[5-7] Although the effectiveness of the short stretch bandage might be influenced by ankle joint mobility,[1] we found no significant interaction in our meta-analysis. Most patients in the dataset (98%), however, were mobile. Previous findings have indicated that the distinction that enables prediction of healing is fixed versus non-fixed joint.[5]

Strengths and weaknesses

A major strength of this research is the degree of rigour using methods proposed by the Cochrane Collaboration for conducting systematic reviews of interventions and the Cochrane IPD Meta-analysis Methods Group.[8 9]

All trials used non-blinded assessment of healing. While it is not possible to define the direction or degree of bias from this the potential for bias should not be overlooked. We could not include two trials with unavailable data. These trials, however, accounted for less than 10% of known randomised patients, and the retrieval of around 90% means that the estimate generated can be viewed with confidence.

Conclusions

Findings suggest that patients with venous leg ulcers treated with four layer bandages experience faster healing than those treated with short stretch bandages. Patients with larger ulcers, older ulcers, and recurrent wounds have poorer healing prognosis regardless of treatment. These data suggest that the observed benefits are consistent despite differences in prognosis. Available data from two trials did not suggest a difference in the adverse event profiles of the two bandage types. Further research is required on related outcomes such as ulcer recurrence, change in ulcer area both as a predictor and as an outcome, and cost effectiveness. Future trials should incorporate blinded outcome assessment.

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Ethical approval: Not required.

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Incidence of cervical cancer after several negative smear results by age 50: prospective observational study

Matejka Rebolj,[1] Marjolein van Ballegooijen,[1] Elsebeth Lynge,[2] Caspar Looman,[1] Marie-Louise Essink-Bot,[1] Rob Boer,[1] Dik Habbema[1]

EDITORIAL by Strander

[1]Erasmus MC, Department of Public Health, PO Box 2040, 3000 CA Rotterdam, Netherlands
[2]University of Copenhagen, Institute of Public Health, PO Box 2099, 1014 Copenhagen K, Denmark
Correspondence to: M Rebolj
m.rebolj@pubhealth.ku.dk

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ABSTRACT

Objective To determine the incidence of cervical cancer after several negative cervical smear tests at different ages.

Design Prospective observational study of incidence of cervical cancer after the third consecutive negative result based on individual level data in a national registry of histopathology and cytopathology (PALGA).

Setting Netherlands, national data.

Population 218 847 women aged 45-54 and 445 382 aged 30-44 at the time of the third negative smear test.

Main outcome measures 10 year cumulative incidence of interval cervical cancer.

Results 105 women developed cervical cancer within 2 595 964 woman years at risk after the third negative result at age 30-44 and 42 within 1 278 532 woman years at risk after age 45-54. During follow-up, both age groups had similar levels of screening. After 10 years of follow-up, the cumulative incidence rate of cervical cancer was similar: 41/100 000 (95% confidence interval 33 to 51) in the younger group and 36/100 000 (24 to 52) in the older group (P=0.48). The cumulative incidence rate of cervical intraepithelial neoplasia grade I+ was twice as high in the younger than in the older group (P<0.001).

Conclusions The risk for cervical cancer after several negative smear results by age 50 is similar to the risk at younger ages. Even after several negative smear results, age is not a good discriminative factor for early cessation of screening.

INTRODUCTION

The debate on early cessation of cervical cancer screening for women with several consecutive negative smear results and no abnormalities by age 50 has been ongoing for 15 years, with no clear conclusions in terms of a change to guidelines. Several authors have studied this issue by analysing the detection rates of preinvasive cervical lesions in these women.[1-9] In general, they observed considerably lower detection rates than in similarly screened younger women. On the basis of this finding they argued that continued screening in this particular group of women is not as efficient as screening among younger women and could be stopped at the expense of only a limited increase in the incidence of cervical cancer among these older women.[2469] This could result in considerable savings for the screening programmes. In the Netherlands it would apply to about half of the women attending screening around age 50.[10]

Because there is strong evidence that cervical intraepithelial neoplasia lesions have a higher probability of progressing to invasive cancer in older women,[11 12] a lower detection rate after age 50 alone does not represent conclusive evidence for lower screening efficiency. Data on invasive cancer have since become available in a Dutch nationwide pathology registry with screening histories linked to diagnostic histological outcomes at the individual level. We measured the incidence of invasive cancer after several consecutive negative smear results in women around age 50 and in younger women.

METHODS

Data

From the Dutch nationwide network and registry of histopathology and cytopathology (PALGA), we retrieved information on all cervix uteri cytological and histological tests until 31 March 2004. The registration began in the late 1970s and achieved practically complete coverage of pathology laboratories in 1990.[13] The retrieved file contained data for all but one pathology laboratory, accounting for less than 1% of smears taken yearly. In the Netherlands, cervical cancer screening became widespread after an extensive pilot project that started in 1976. In 2003, 77% of women at risk (that is, those with a cervix) between ages 30 and 60 had had at least one smear in the preceding five years.[14]

In the network, women are identified through their birth date and the first four letters of their family name enabling linkage of the tests belonging to the same woman. Because this code is not always unique, it introduces an upward bias in the incidence after a negative screen. To avoid this bias, we excluded women with 0.5% of the most common first four letters of the family name—that is, about 30% of women.

Final diagnoses for all non-cancer excerpts (all cytology and non-cancer biopsies) were based on the SNOMED oriented codes. We identified cases of cervical cancer by checking the pathology reports for all excerpts that included codes for cervical cancer for the period 1994-2002.

Statistical analysis

We selected women in two age groups, 45-54 and 30-44 if they had a third consecutive negative primary smear result in this age interval at any time since the beginning of the registration. Women with previous histological or cytological abnormalities were

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Table 1 | Incidence of invasive cervical cancer after third consecutive negative smear result for two age groups

Time (years) since third negative smear	Age (years) at entry: 30-44			45-54			P value‡
	Woman years*	Women with invasive cancer	Cumulative incidence rate† (95% CI)	Woman years*	Women with invasive cancer	Cumulative incidence rate† (95% CI)	
≤1	324 512	4	1 (0 to 3)	172 920	3	2 (1 to 5)	0.66
>1-<3	628 471	16	6 (4 to 10)	344 825	16	11 (7 to 17)	0.09
≥5-<10	563 725	27	16 (12 to 21)	304 194	5	14 (10 to 21)	0.65
≥10-<15	837 359	43	41 (33 to 51)	378 075	13	36 (24 to 52)	0.48
≥15-<20	200 225	11	70 (51 to 95)	65 373	4	73 (39 to 135)	0.85
≥20	41 672	4	128 (79 to 207)	13 145	1	105 (50 to 219)	0.27
Total	2 595 964	105	—	1 278 532	42	—	—

*Accrued between 1 January 1994 and 31 December 2002.
†Per 100 000 women.
‡Two sided, for difference in rate between two age groups at specific time points.

excluded. Women were followed up from the date of the third negative smear until the date of the first diagnosis of cervical cancer or until the end of 2002, whereas follow-up was left censored at the beginning of 1994.

We first calculated the cumulative incidence rate of cervical cancer in the period 1994-2002 by time since the third negative result. For most women a maximum of 10 years of follow-up was available. We tested the difference in the rate between the age groups. Secondly, we tested the difference in the incidence rates between the two age groups during the whole follow-up period (the hazard rate). We tested time dependency of relative hazards.

RESULTS

We identified 218 847 women in the older group and 445 382 in the younger group who met our inclusion criteria. In the period between 1 January 1994 and 31 December 2002, 1.3 and 2.6 million person years in follow-up accrued in these groups, respectively, an average of 5.84 and 5.83 years per woman (table 1). The two groups had a similar rate of screening after the third negative smear: about a third had none, about a third had one, and the remaining third had more than one further primary test registered. Forty two women in the older group and 105 women in the younger group developed cervical cancer (table 1).

During follow-up, the difference in the cumulative incidence rate between the age groups was never significant (table 1). The average age of women was 37.3 years in the younger group and 48.7 years in the older group. The overall hazard ratio was 0.84 (95% confidence interval 0.59 to 1.21) for the older compared with the younger group. The test for time dependency of the relative hazards was non-significant (P=0.86).

We calculated the cumulative incidence rate with cervical intraepithelial neoplasia grade I+ as the end point (table 2). By 10 years, the cumulative incidence rate was 1258/100 000 (1209 to 1308) in the younger group and 594/100 000 (547 to 645) in the older group. The difference between both groups was significant throughout the entire follow-up. The cumulative incidence rate of cervical intraepithelial neoplasia grade II+ was 721/100 000 (684 to 759) among younger and 258/100 000 (227 to 293) among older women. The cumulative incidence rate of cervical intraepithelial neoplasia grade III+ was 445/100 000

Table 2 | Incidence of cervical intraepithelial neoplasia I+ (CIN I+) after third consecutive negative smear result for two age groups

Time (years) since third negative smear	Age (years) at entry: 30-44			45-54			P value‡
	Woman years*	Women with CIN I+	Cumulative incidence rate† (95% CI)	Woman years*	Women with CIN I+	Cumulative incidence rate† (95% CI)	
≤1	324 381	233	72 (63 to 82)	172 850	90	52 (42 to 64)	0.008
>1-<3	627 524	584	258 (241 to 277)	344 441	172	152 (135 to 172)	<0.001
≥5-<10	561 412	834	555 (529 to 583)	303 363	240	310 (284 to 339)	<0.001
≥10-<15	829 336	1192	1258 (1209 to 1308)	375 786	224	594 (547 to 645)	<0.001
≥15-<20	196 753	197	1707 (1622 to 1796)	64 635	30	769 (686 to 862)	<0.001
≥20	40 898	24	1986 (1841 to 2143)	12 995	5	920 (772 to 1096)	<0.001
Total	2 580 304	3064	—	1 274 070	761	—	—

*Accrued between 1 January 1994 and 31 December 2002.
†Per 100 000 women.
‡Two sided for difference in rate between two age groups at specific time points.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The detection of cervical intraepithelial neoplasia in adequately screened women with several consecutive negative smear results by age 50 is considerably lower than among younger similarly screened women

The probability of progression of a cervical intraepithelial neoplasia lesion to cervical cancer increases by age

WHAT THIS STUDY ADDS

The risk for cervical cancer after several negative smear results by age 50 is similar to that at younger ages

It is therefore not consistent to stop screening women with several consecutive negative smears after age 50

(417 to 476) among younger and 165/100 000 (140 to 194) among older women.

DISCUSSION

The relative risk of developing cervical cancer after a third consecutive negative smear result among women around age 50 did not differ significantly from the risk in younger women. This outcome was not biased by differential screening during follow-up because there was no difference between the age groups in this respect. After several consecutive negative results the screening efficiency in terms of detection and prevention of cervical cancer is at the same level around age 50 as it is at younger ages.

In the analysed age groups (30-54 years), the incidence rate of cervical cancer in the general population was between 10 and 14 per 100 000 woman years in the period 2001-5.[15] Whether the relatively low incidence rates observed in our well screened study groups warrant continued screening should be determined by subsequent analyses.

We observed a lower risk for cervical intraepithelial neoplasia grades I+, II+, and III+ in the older group. In this respect, our results are consistent with those of others,[2 4 6] and confirm that cervical intraepithelial neoplasia is not an accurate intermediate end point for the question addressed.

Because we included women as soon as they had the third consecutive negative result, younger women will on average have been screened more intensely at a younger age than women included in the older group; the older women might therefore be at higher risk. The selection criterion of being disease free on three consecutive screenings, however, and the finding that the screening attendance after the third negative result was similar in both groups make such a bias unlikely.

We selected women with negative screening histories. In our data, inclusion of women with screen detected abnormalities followed by three consecutive primary negative results did not affect the two age groups differently: the cumulative incidence rate at 10 years was 42 (30 to 57)/100 000 in the older group and 42 (34 to 51)/100 000 in the younger group.

Implications of the study

The similarity in the cumulative incidence rate between the two age groups is not unexpected given the observed age specific incidence before screening became widespread.[16] In several Western European countries, the incidence before screening rose rapidly to a peak around ages 44-49 and declined thereafter. Thus, when women in the 30-44 year group are ageing, they proceed from a lower to a higher risk age. The opposite is true for women in the 45-54 year group. This translates into roughly equal levels of cumulative incidence rate for cancer during the first 10 years for the two age groups.[16]

Our data do not permit a simple extension of our study to older ages. For example, in 79 586 women satisfying the criteria at ages 55-64, the 10 year cumulative incidence rate was 47/100 000 (23 to 99) and was statistically comparable with that in women below age 55. Women aged 55 or older, however, had a considerably lower screening intensity after the third negative result. This diminishes the comparability with women below that age.

The continued risk for cervical cancer is consistent with the considerable rate of incident human papillomavirus (HPV) infections throughout the age span we focused on.[17 18] As it is the screen detected cervical intraepithelial neoplasia rather than an HPV infection that can be treated, HPV screening instead of cytological screening could eliminate relatively few extra HPV infections before the age of 50. In case of HPV screening, our conclusions would therefore remain the same.

Conclusions

Using invasive cancer as the relevant end point our conclusion that it would not be consistent to stop screening women with several negative smear results by age 50 while not also relaxing the screening policy for younger women with similar screening histories lends support to the current cervical cancer screening guidelines in England and other developed countries,[19-23] which do not discriminate women by age up to 60-65. Whether individual tailoring of recommendations for further screening based on screening histories would be an efficient alternative to the current fixed schedule in any age group remains to be explored.

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RB has been participating since 1989 in the screening research group at the department. He has been affiliated with RAND since 2000. Since 2007, he has been a director of evidence based strategies-disease modelling and economic evaluation at Pfizer, who develop and sell various drugs for cancer and other diseases. This research and manuscript were neither funded nor supported by Pfizer.

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Modifiable factors influencing relatives' decision to offer organ donation: systematic review

Arabella L Simpkin, Laura C Robertson, Vicki S Barber, J Duncan Young

EDITORIAL by Shafer

Intensive Care Society Clinical Trials Group, Kadoorie Centre, John Radcliffe Hospital, Headington, Oxford OX3 9DU

Correspondence to: J D Young
duncan.young@nda.ox.ac.uk

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ABSTRACT

Objective To identify modifiable factors that influence relatives' decision to allow organ donation.

Design Systematic review.

Data sources Medline, Embase, and CINAHL, without language restriction, searched to April 2008.

Review methods Three authors independently assessed the eligibility of the identified studies. We excluded studies that examined only factors affecting consent that could not be altered, such as donor ethnicity. We extracted quantitative results to an electronic database. For data synthesis, we summarised the results of studies comparing similar themes.

Results We included 20 observational studies and audits. There were no randomised controlled trials. The main factors associated with reduced rates of refusal were the provision of adequate information on the process of organ donation and its benefits; high quality of care of potential organ donors; ensuring relatives had a clear understanding of brain stem death; separating the request for organ donation from notification that the patient had died; making the request in a private setting; and using trained and experienced individuals to make the request.

Conclusions Limited evidence suggests that there are modifiable factors in the process of requests for organ donation, in particular the skills of the individual making the request and the timing of this conversation, that might have a significant impact on rates of consent. Targeting these factors might have a greater and more immediate effect on the number of organs for donation than legislative or other long term strategies.

INTRODUCTION

The greatest identified impediment to organ donation from patients after brain stem death on an intensive care unit in the UK is refusal of consent by the relatives of the donor.[1-3 w2] A recent audit of all deaths in 341 intensive care units in the UK over a 33 month period

showed that 41% of the relatives of potential organ donors refused to consent to donation.[4]

Although the Human Tissue Act 2004,[5] prioritises the wishes of the potential donor over the relatives, it is almost inconceivable that organs would be retrieved from a brain stem dead patient against the wishes of his or her family, so the consent of relatives will remain important.

Interviews with the relatives of brain stem dead patients have shown that about a third of those who refused donation would not make the same decision again,[w3] whereas few consenting relatives regretted their decision, suggesting that many decisions to refuse to allow donation are not based on deeply held religious or other views. We reviewed published peer reviewed studies to identify any modifiable factors in the request for organ donation that might increase consent rates.

METHODS

Searching—On 8 May 2008 we searched Medline, Embase, and CINAHL. We used the search terms "organ" or "tissue" and "don*" or "consent" without language restrictions. We hand searched reference lists of included studies.

Inclusion and exclusion criteria—We included studies that reported modifiable factors associated with the consent outcome of a request for organ donation to the relatives of a beating heart potential organ donor (a patient meeting the criteria for brain stem death). We included all studies containing data, whether from observational or interventional studies.

Validity assessment and data abstraction—Three authors screened the obtained titles and abstracts for eligibility and obtained relevant full text articles.

Data synthesis—We reviewed papers to identify all the modifiable factors associated with agreement or refusal of consent. We report common themes in narrative form under thematic headings.

RESULTS

Trial flow—Database searching produced a list of 22 032 publications. Of these, we excluded 21 786. We reviewed 246 full papers. After we excluded 226 papers that did not meet the inclusion criteria, we included 20 studies in the review.[w1-w20]

Study characteristics—The studies identified were of two types. In observational studies the proportion of successful requests for organ donation was determined when the factor was present and compared with the proportion when it was not. In "before and after" audits the factor was modified and the effect on subsequent organ donation noted. We did not identify any randomised controlled trials.

Data synthesis—We identified modifiable factors that apparently influence relatives' decisions to allow organ donation into six categories: information discussed during the request; perceived quality of care of the donor; understanding of brain stem death; specific timing of the request; setting in which the request is made; and approach and expertise of the individual making the request. We present all the modifiable factors identified in studies with a P value of ≤0.05 for differences in the proportion of relatives giving consent to organ donation with the factor present or absent. We also present modifiable factors for which no statistical results were reported but which the authors considered relevant.

Information discussed during request—Five studies retrospectively collected data via chart reviews and interviews with staff and families in an attempt to establish whether information provided during the request process was associated with the family's decision to donate or not donate organs for transplantation.[w1 w3 w5 w18 w20] Siminoff et al studied 420 donor eligible patients.[w1 w20] Factors correlating with consent to organ donation were delivery of information on the costs of donation; the impact of donation on funeral arrangements; and assurances that the family had a choice about which organs to donate. When healthcare professionals mentioned that donation had the potential to help others, families were also more likely to donate, but telling families that they were required to ask about donation had a negative impact on consent rates.[w1] The other papers showed a significantly higher rate of consent when families thought they had been given enough information to make an informed decision about organ donation.[w3 w5 w18 w20]

Perceived quality of care of donor—Perceived quality of care during the hospital stay had a significant impact on consent rates in the three papers that examined this.[w1 w3 w4] All three papers showed that a negative perception of care results in a decreased rate of consent.

Understanding of brain stem death—In five papers there was a significant association between understanding and consent to organ donation,[w1 w3-w6] with a sixth paper showing a non-significant increase in consent in families who understand brain stem death but a significant difference in consent rates in families accepting the concept of brain stem death.[w19] In a review of 285 families, 71% that had complete knowledge of brain stem death agreed to donation compared with only 29% of those with incomplete or inaccurate knowledge of brain stem death.[w4] When families were asked if they agreed that people cannot recover when they are brain dead, 80% of donor family respondents correctly agreed with this statement, while only 48% of the non-donor family group did so.[w3]

Timing of the request—A series of nine reports all suggested that there is an improved rate of consent when there is temporal separation ("decoupling") between notification and acceptance of brain stem death and request for donation.[w1-w4 w7-w9 w14 w18] The most important factor seems to be that the request for donation does not occur at the same time as the notification of death or testing for brain stem death. Niles and Mattice determined that the consent rate was similar regardless of whether families were approached either before (62%) or after (57%) death but much lower when donation was mentioned at the time of the death notification (25%).[w9] Giving families enough time to make a

Duncan Young talks about this paper in the BMJ Podcast

WHAT IS ALREADY KNOWN ON THIS TOPIC

There is a severe shortage of organs for transplantation

The largest impediment to organ procurement is relatives' refusal

WHAT THIS STUDY ADDS

The timing of the request and the person making the request have a significant impact on consent rates

Modifying the consent request process might be the fastest way to increase organ donation rates

These changes could be implemented without undue delay in the UK

decision was also important.[w1 w3 w4 w18] In a study that retrospectively interviewed the next of kin of 164 potential organ donors, 83% of donor and 56% of non-donor family respondents said that they were given enough time to understand that their relative was dead before medical staff brought up organ donation.[w3]

Setting in which the request is made—Evidence that a private location for discussion about organ donation improves consent rates is clearly documented.[w2 w3] In two studies consent rates for requests made in settings that provided little privacy (requests made by telephone, in the patient's room, at the nursing station, or in the hallway) were 45% and 30% compared with consent rates of 56% and 52% in more private settings.[w2 w3] One study showed no significant benefit of a private setting for organ donation requests.[w20]

Approach and expertise of the person making the request—The most studied factor influencing consent is the approach and expertise of the person making the request. Fourteen studies investigated this.[w1-w5 w7 w10-w17] Differences in consent rates seem to be associated with which professionals are involved with the request process.[w1 w2 w4 w7 w10 w11] In a study of 707 requests for organ donation, a combined approach by hospital staff and coordinators from an organ procurement organisation (OPO) resulted in a consent rate of 72%. Hospital staff alone had a consent rate 53%, while coordinators alone had a consent rate 62%.[w2] Families have reported that conversations with OPO staff were crucial to their donation decision. Talking to a member of OPO staff before being asked to make a decision and spending more time with a member of OPO staff were both strongly associated with donation.[w1] There is a correlation between staff training in effective procedures for requesting organ donation and donation rates.[w14-w16] In hospitals with high rates of organ donation, 53% of the staff had received training compared with 24% of staff in hospitals with low rates of organ donation.[w14] Finally, it seems that courtesy increases organ donation rates.[w5]

DISCUSSION

The main modifiable factors significantly associated with whether relatives deny or allow organ donation were information discussed during the request, perceived quality of care of the donor, understanding of brain stem death, specific timing of the request, setting in which the request is made, and the approach and skill of the individual making the request. Ensuring that adequate time is available both to make the request and to allow families to consider the request also seems important.

Limitations and strengths

Our review will identify only those factors that have been studied and reported and only those at the level of individual requests. Factors modifiable at a population level, such as the fraction of the population participating in an organ donor register, and some factors modifiable at a hospital level, such as local donation champions, did not appear in the identified studies. Many of the studies identified were retrospective reviews of medical records. There was a large reliance on hospital or OPO staff as data collectors, who might not be unbiased observers. Most of the studies were based on small numbers, and there were no randomised controlled studies from which to draw data. Several of the studies were based on structured interviews with donor and non-donor families, with little detail on whether the sample interviewed are representative of the whole. These interviews were based on family recollections and thus are accurate only to the extent that their memories of these events are accurate, introducing recall bias. Finally, as the studies are observational, factors correlated with consent to organ donation might not be causative.

The two factors that had the largest effect on consent rates were the person making the request and the timing of this conversation. Consent rates were higher when the request was made by the organ procurement coordinator (donor transplant coordinator in the UK) in conjunction with hospital staff members. Clearly, it is not possible to place a dedicated donor transplant coordinator in every hospital, but it might be possible to consider this in hospitals with larger numbers of potential organ donors. UK Transplant, which provides support to transplant services in the UK, has adopted this strategy.

There is a need for large rigorously conducted intervention studies to test the factors that might be modified to increase organ donation.

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