Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT

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Declared competing interests of authors: Matthew L Costa is a member of the general board for the Health Technology Funding stream. Keith Willett received royalty payments from Zimmer for implant design outside the submitted work. Sarah E Lamb is a member of the Health Technology Assessment (HTA) Additional Capacity Funding Board, HTA End of Life Care and Add-on Studies, HTA Prioritisation Group and HTA Trauma Board.

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published December 2018
DOI: 10.3310/hta22730

Scientific summary

The WOLLF randomised controlled trial

Health Technology Assessment 2018; Vol. 22: No. 73
DOI: 10.3310/hta22730

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Scientific summary

Background

Fractures of the lower limb are common injuries in civilian and military populations. Most fractures are 'closed', that is, the skin overlying the fracture is intact. However, if the fracture is 'open' then the broken bone is exposed to contamination and the risk of infection is greatly increased. In severe, high-energy open fractures of the lower limb, infection rates of 27% are still reported, even in specialist trauma centres. The initial management of open fractures involves the surgical removal of damaged tissue and contamination (debridement) under anaesthetic and the administration of antibiotics. The fracture is usually immobilised with some form of internal or external fixation and a dressing is applied to the surface of the wound.

Traditionally, a sealed, non-adhesive layer is applied to the exposed area to protect the open fracture from further contamination. The wound is covered in this way until a reassessment and further debridement are performed in the operating theatre 48–72 hours later. This method has been used throughout the NHS and in military practice for many years.

Negative-pressure wound therapy (NPWT) is an alternative form of dressing which may be applied to open-fracture wounds. This device creates a vacuum that removes blood and exudate that may collect in the wound and pose an infection risk. The vacuum may also remove bacteria from the wound and encourage the formation of 'granulation' (healing) tissue. However, NPWT dressings and the vacuum machines are considerably more expensive than traditional wound dressings.

Previous trials of NPWT have shown encouraging results, suggesting lower infection rates in other patient populations. However, before this trial, there was only one randomised controlled trial (RCT) comparing standard wound dressing with NPWT for patients with open fractures of the lower limb (Stannard JP, Volgas DA, Stewart R, McGwin G Jr, Alonso JE. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009;**23**:552–7). That trial demonstrated a lower rate of infection in patients treated with NPWT but included only 59 patients at a single trauma centre. Despite the lack of strong evidence, clinical guidelines around the world rapidly incorporated the use of NPWT for open-fracture wounds.

The aim of this pragmatic, multicentre RCT was to compare standard wound dressings with NPWT for adults with an open fracture of the lower limb.

Methods

Study design

The study was conducted in two phases. Phase I assessed the feasibility of running a large-scale multicentre RCT in the challenging environment of trauma care. The feasibility study was undertaken in five trauma centres in England over a 6-month period. Qualitative interviews were conducted with 20 patients, while two multidisciplinary focus groups were held with staff to inform recruitment and consent procedures. Phase II consisted of the main RCT, in which participants were recruited from 24 specialist trauma hospitals in the UK Major Trauma Network.

Patients

Eligible patients were aged ≥ 16 years and had an open fracture of the lower limb assessed as Gustilo and Anderson (G&A) grade 2 or 3. Patients had to present to the trial hospital within 72 hours of their injury, including those who were transferred from other hospitals. Patients were excluded if they had

contraindications to anaesthesia or were unable to adhere to trial procedures or complete questionnaires, for example patients with permanent cognitive impairment.

Interventions

Usual-care group

Usual care for open fractures is a standard dressing comprising a non-adhesive layer applied directly to the wound covered by a sealed dressing or bandage. The standard dressing did not use 'negative pressure'. The exact details of the materials used were left to the discretion of the treating surgeon as per routine care. Details of each dressing applied in the trial were recorded and classified according to *British National Formulary* classification.

Intervention group: negative-pressure wound therapy

The NPWT dressing used an 'open-cell' solid foam or gauze which was laid onto the wound followed by an adherent, sealed dressing. A sealed tube was connected from the dressing to a pump which created a partial vacuum over the wound. The basic features of the NPWT are universal, but the exact details of the dressing and pressure (mmHg) were left to the discretion of the treating health-care team. Details of dressings used were recorded in trial documentation.

Outcomes

The primary outcome was the Disability Rating Index (DRI) score, a validated scale which assessed patients' rating of their own disability in the 12 months after randomisation. The DRI provides a 100-point score, where 0 represents normal function and 100 represents complete disability.

The secondary outcomes were health-related quality of life (HRQoL), deep surgical site infection (SSI), other postoperative complications and resource use. Infection outcomes and complications were assessed by independent research staff. A photographic assessment of wound healing was made at 6 weeks. Radiographic images were collected at 6 weeks and 12 months. Patient-reported outcomes (DRI; EuroQol-5 Dimensions, three-level version; and Short Form questionnaire-12 items), self-reported complications and health-care resource use were collected by questionnaire at baseline, 3, 6, 9 and 12 months after randomisation.

Care pathway

In the UK Major Trauma Network, most patients with an open fracture of the lower limb are transported directly to a specialist trauma hospital (a major trauma centre or a trauma unit with orthoplastic surgeons on site) for definitive care. Patients presenting to a non-specialist hospital are usually transferred within 72 hours of their injury. Usual care for patients admitted with an open fracture of the lower limb involves surgery on the next available trauma operating list. All patients received a general or regional anaesthetic. The wound associated with the fracture was 'debrided' (surgical removal of damaged tissue and contamination) in the operating theatre and the fracture treated with either internal or external fixation. At the end of the initial operation, if the wound could not be closed primarily (direct suture of the wound edges), patients were randomised and allocated to either standard dressing or NPWT.

After treatment allocation, both groups of patients then followed the normal postoperative management pathway for patients with an open fracture of the lower limb. This usually involved a second operation at 48–72 hours, at which time a further wound assessment and debridement were performed and the wound closed either primarily or by soft-tissue reconstruction as necessary. In some cases, it is not safe to perform definitive closure of the wound within 72 hours. For example, some patients with a serious head injury in association with their open fracture of the lower limb cannot tolerate a long anaesthetic and surgical procedure such as a 'free-flap' reconstruction. If the wound could not be closed definitively, a further dressing was applied to the open-fracture wound after the second debridement. Any further wound dressing followed the allocated treatment until definitive closure/cover of the wound was achieved.

Randomisation and allocation sequence generation

Randomisation was based on a computer-generated randomisation algorithm held and controlled by York Clinical Trials Unit. The unit of randomisation was the individual patient on a 1 : 1 basis and then stratified by trial centre and G&A grade. When a patient entered the trial, non-identifiable details were logged on the secure, encrypted, web-based system. Information included patient initials, date of birth, gender and eligibility checks.

Participants were assigned to their treatment allocation intraoperatively at the end of initial surgery, but before any wound dressing was applied.

Blinding

It was not possible to blind trial participants to treatment allocation as wound dressings were clearly visible. In addition, the treating surgeons could not be blind to the intervention, but the surgical and health-care team were not involved in trial assessments. Patient-reported outcomes were collected by postal questionnaire and returned directly to the central trial office (Warwick Clinical Trials Unit). Wound photographs were taken by research staff at the 6-week follow-up clinic. Wound images were reviewed independently by two experienced assessors blind to treatment allocation.

Statistical analysis

The main analysis investigated differences in the primary outcome measure, the DRI score at 1 year after injury, between the two treatment groups (standard wound dressings and NPWT) on an intention-to-treat (ITT) basis. Early and mid-term status was assessed and reported at 3, 6 and 9 months.

Health economic analysis

An economic evaluation was conducted from the recommended NHS and Personal Social Services perspective. An incremental cost-effectiveness analysis was performed, expressed in terms of incremental cost per quality-adjusted life-years (QALYs) gained. A bivariate regression of costs and QALYs, with multiple imputation of missing data, was conducted with the view to estimating the incremental cost per QALY gained associated with NPWT dressings. Sensitivity analyses were undertaken to assess the impact of uncertainty surrounding aspects of the economic evaluation, while prespecified subgroup analyses were conducted to explore the effects of heterogeneity in the trial population.

Results

Patients

A total of 625 patients were randomised into the trial between July 2012 and December 2015. Of these, 460 patients were willing and able to provide informed consent.

Primary outcome

There was no evidence of a difference in the DRI at 12 months between those patients treated with NPWT and those treated with standard wound dressings. The mean DRI in the NPWT group was 45.5 points [standard deviation (SD) 28.0 points] versus 42.4 points (SD 24.2 points) in the standard dressing group, giving a difference of –3.9 points [95% confidence interval (CI) –8.9 to 1.2 points] in favour of standard dressings ($p = 0.132$). As the minimal clinically important difference for the DRI is 8 points, we conclude that it is extremely unlikely that NPWT dressings confer a clinically important difference in DRI scores for patients with an open fracture of the lower limb. Similarly, there was no evidence of a difference in DRI score at 3, 6 or 9 months.

The secondary per-protocol (per treatment) analysis of the DRI did not differ from the primary ITT analysis, the difference between groups being –4.0 points (95% CI –9.1 to 1.0 points) in favour of the standard dressings ($p = 0.119$). This was as expected because the number of patients who did not receive the treatment allocated within the trial was small.

Secondary outcomes

The main conclusion of the trial is supported by the analyses of the secondary outcome measures. There was no evidence of a difference in the HRQoL scores between the treatment groups at any point in the 12 months following the injury. The mean EuroQoL-5 Dimensions (EQ-5D) score in the NPWT group was 0.55 (SD 0.33) versus 0.56 (SD 0.32) in the standard dressing group, giving a difference of 0.01 (95% CI –0.06 to 0.07) in favour of the standard dressing ($p = 0.823$).

There was no difference in the number of deep SSIs between the treatment groups. In total, 35 out of the 460 participants (7.6%) had an indication of a deep SSI: 16 (7.1%) in the NPWT group and 19 (8.1%) in the standard dressing group, giving an estimated odds ratio of 1.18 (95% CI 0.59 to 2.37) in favour of NPWT ($p = 0.638$).

In terms of the economic evaluation, the base-case analysis used multiply imputed data and produced an incremental cost-effectiveness ratio of £267,910 per QALY gained, reflecting, on average, substantially higher costs and only marginally higher QALYs in the NPWT group. The probability that NPWT is cost-effective in this patient population did not exceed 27% regardless of the value of the cost-effectiveness threshold.

Discussion

This trial provides no evidence of a difference in the DRI between those patients treated with NPWT and those treated with standard wound dressings following an open fracture of the lower limb. Contrary to the existing evidence, there was no difference in the rate of deep SSI. Nor was there any evidence of a difference in HRQoL at any point in the first 12 months after the injury. NPWT did not reduce the cost of treatment and was associated with a low probability of cost-effectiveness.

In conclusion, contrary to the existing literature and current surgical guidelines, NPWT does not provide a clinical or economic benefit for patients with an open fracture of the lower limb.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN33756652 and UKCRN Portfolio ID 11783.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/57/20. The contractual start date was in April 2012. The draft report began editorial review in April 2017 and was accepted for publication in July 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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